UNIVERSIDADE FEDERAL DE SÃO PAULO

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SOBREPESO E OBESIDADE NO DIABETES MELLITUS DO TIPO 1: PREVALÊNCIA E FATORES RELACIONADOS

FERNANDO VALENTE

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Orientador: Prof. Dr. Sérgio Atala Dib
Co-orientador: Prof. Dr. João Roberto de Sá
Coordenadora do Programa: Profa. Dra. Marise Lazaretti-Castro

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Co-Orientador:

Prof. Dr. João Roberto de Sá

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Sumário

1. Abreviaturas

CHO: Carboidrato

DCCT: do inglês *Diabetes Control and Complication Trial*

DCV: Doença Cardiovascular

DM: Diabetes Mellitus

DM1: Diabetes Mellitus do Tipo 1

DM2: Diabetes Mellitus do Tipo 2

DRC: Doença renal crônica

DVP: Doença vascular periférica

EDIC: do inglês *Epidemiology of Diabetes Interventions and Complications*

eGDR: do inglês *Estimated Glucose Disposal Rate*

eIS-CACTI: do inglês *Insulin Sensitivity prediction equation, from the Coronary Artery Calcification in Type 1 Diabetes*

FTO: do inglês *Fat mass and obesity associated gene*

GAD: Descarboxilase do ácido glutâmico

HAS: Hipertensão arterial sistêmica

HbA1c: Hemoglobina glicada

HDL: do inglês *High Density Lipoproteins*

HF: História familiar

HLA: Antígeno de leucocitários humanos

HMW adipo: do inglês *High Molecular Weight Adiponectin*

HOMA-IR: do inglês *Homeostasis Model Assessment-Insulin Resistance*

IA2: do inglês *Islet antigen-2*

IDF: do inglês *International Diabetes Federation*

IMC: Índice de Massa Corporal

IL-1: Interleucina-1

IL-6: Interleucina-6

PA: Pressão arterial

RCQ: Relação cintura-quadril

SM: Síndrome metabólica

SNP: do inglês *Single Nucleotide Polimorfism*

TNF-alfa: Fator de Necrose Tumoral alfa

ZnT8: Transportador de zinco

2. Apresentação

Nesta tese de mestrado apresentamos, de acordo com as recomendações da Câmara de Pós-graduação da Universidade Federal de São Paulo, Escola Paulista de Medicina, um trabalho completo em inglês (Artigo 1), intitulado *"**Parents' cardiovascular risk factors are related to overweight and obesity in young Brazilians with type 1 diabetes**"*, publicado como Artigo Original para a revista ***Journal of Diabetes and its Complications.***

A obesidade é um emergente problema de saúde pública na população geral e em indivíduos com diabetes mellitus do tipo 1 (DM1) (artigo 2) pela sua prevalência crescente e correlação como um dos fatores de risco de doença cardiovascular (DCV).

Entretanto, os fatores relacionados à obesidade no DM1 não estão tão estudados como na população geral e no próprio diabetes mellitus do tipo 2 (DM2). Estes fatores levaram à principal hipótese do estudo desta tese no sentido de colaborar nessa área de pesquisa ainda em formação e de importância inerente, pois o indivíduo com DM1 tem como principal causa de morte, a partir dos 30 anos de idade, a DCV.

Com o aumento da sobrevida das pessoas com DM1, vem ocorrendo um aumento na mortalidade associada à DCV, que pode ser mediada pelo excesso de peso. A observação do crescimento das taxas de sobrepeso e obesidade nos indivíduos com DM1, também no nosso meio, nos estimulou a identificar os principais fatores de risco para o ganho de peso, incluindo fatores de risco cardiovascular nos familiares e se haveria alguma implicação do sobrepeso e da obesidade em outros parâmetros clínicos e metabólicos conhecidamente correlacionados a um maior risco de DCV, dando subsídios para a prevenção tanto da obesidade quanto da DCV na abordagem dos indivíduos com DM1.

3. Resumo/Abstract

Objetivo: Identificar as características do histórico familiar e os fatores de risco para doença cardiovascular (DCV) associados ao sobrepeso e à obesidade em brasileiros com diabetes tipo 1 (DM1).

Métodos: Realizamos análises antropométricas e laboratoriais transversais em jovens com DM1, divididos segundo o status de IMC em peso normal, sobrepeso ou obesidade, e em controles voluntários sem doenças crônicas e sem história familiar de diabetes.

Resultados: Dos 181 participantes com DM1 (idade média de 23.6 ± 5.5 anos), 87 eram mulheres e 94 homens (64%/78% peso normal, 27%/15% sobrepeso e 9%/7% obesidade). Em relação aos homens com sobrepeso e peso normal, os com obesidade tinham idade maior (29.4±3.7 vs 23.2±5.8 vs 22.5±5.3 anos, p=0.01); eram mais propensos a serem negros (57.1% vs 7.1% vs 7.0%); apresentaram níveis mais elevados de triglicerídeos (180±140 vs 74±34 vs 87±57 mg/dL, p=0.03) e pressão arterial (PA) diastólica (85±8 vs 79±9 vs 73±10 mmHg, p=0.01), menor *estimated glucose disposal rate* (eGDR) (5.4±1.9 vs 6.8±1.9 vs 7.9 ± 1.7 mg/kg/min, p<0.01) e maior prevalência de parentes de primeiro grau com hipertensão (100% vs 57.1% vs 50.7%, p=0.03) e DCV precoce (28.6% vs 7.1% vs 2.7%, p=0.02). Mulheres com obesidade e sobrepeso eram mais predispostas a ter menor eGDR (5.4±2.4 vs 6.1±2.1 vs 8±2.1 mg/kg/min, p<0.01), e mulheres com obesidade eram mais propensas a ter um parente de primeiro grau com obesidade (62.5% vs 47.8% vs 25.5%, p=0.03). Não houve diferença na adiponectina de alto peso molecular (HMW adipo) e na visfatina entre os grupos de IMC de pessoas com DM1. Os polimorfismos da visfatina e do *Fat mass and obesity associated gene* (FTO) analisados não foram associados ao excesso de peso no grupo com DM1. Com idade semelhante (23.9±3.5 anos) aos participantes com DM1, os controles tinham menor IMC (21.9±2.3 vs 23.9±4.2 kg/m^2, p<0.01) e circunferência abdominal (75.9±8.2 vs 85.5±10.6 cm, p<0.01), menor PA sistólica (102±12 vs 115±15 mmHg, p<0.01) e diastólica (66±8 vs 74±10 mmHg, p<0.01), maior HDL (64±19 vs 55±15 mg/dL, p<0.01), maior HMW adipo (15.66±12.09 vs 10.35±10.79 µg/mL, p<0.01) e visfatina (6.75±3.69 vs 2.76±2.81 ng/mL, p<0.01).

Conclusão: Um terço dos jovens com DM1 apresentava sobrepeso ou obesidade. O excesso de peso foi associado à história familiar de obesidade para mulheres e história familiar de DCV precoce ou hipertensão para homens. O IMC foi relacionado à diminuição da sensibilidade à insulina em ambos os sexos, mas apenas os homens com DM1 apresentaram comprometimento metabólico. Nossos dados destacam a importância de considerar o histórico familiar em indivíduos com DM1.

Aim: To identify family background characteristics and cardiovascular disease (CVD) risk factors linked to overweight and obesity in Brazilian with type 1 diabetes (T1D).
Methods: We performed cross-sectional anthropometric and laboratory analyses in young individuals with T1D, divided according to BMI status into normal weight, overweight or obesity, and in volunteer controls without chronic diseases and without a family history of diabetes.
Results: Among 181 participants with T1D, mean age of 23.6±5.5 years, 87 were women and 94 were men (64%/78% normal weight, 27%/15% overweight and 9%/7% obese). Compared to overweight and normal weight men, obese men were older (29.4±3.7 vs 23.2±5.8 vs 22.5±5.3 years, p=0.01); were more likely to be Black (57.1% vs 7.1% vs 7.0%); had higher triglyceride levels (180±140 vs 74±34 vs 87±57 mg/dL, p=0.03) and diastolic blood pressure (BP) (85±8 vs 79±9 vs 73±10 mmHg, p=0.01), lower estimated glucose disposal rate (eGDR) (5.4±1.9 vs 6.8±1.9 vs 7.9 ± 1.7 mg/kg/min, p<0.01) and higher prevalence of first-degree relatives (FDR) with hypertension (100% vs 57.1% vs 50.7%, p=0.03) and early CVD (28.6% vs 7.1% vs 2.7%, p=0.02). Obese and overweight women were more likely to have lower eGDR (5.4±2.4 vs 6.1±2.1 vs 8±2.1 mg/kg/min, p<0.01), and obese women were more likely to have FDR with obesity (62.5% vs 47.8% vs 25.5%, p=0.03). There were no differences in *High Molecular Weight Adiponectin* (HMW adipo) and visfatin between the BMI groups of people with T1D. The visfatin and *Fat mass and obesity associated gene* (FTO) polymorphisms analyzed were not associated with excess weight in this group with DM1. At a similar age (23.9±3.5 years) to people with T1D, controls had lower BMI (21.9±2.3 vs 23.9±4.2 kg/m^2, p<0.01) and waist circumference (75.9±8.2 vs 85.5±10.6 cm, p<0.01), lower SBP (102±12 vs 115±15 mmHg, p<0.01) and DPB (66±8 vs 74±10 mmHg, p<0.01), higher HDL (64±19 vs 55±15 mg/dL, p<0.01), higher HMW adipo (15.66±12.09 vs 10.35±10.79 µg/mL, p<0.01) and visfatin (6.75±3.69 vs 2.76±2.81 ng/mL, p<0.01).
Conclusion: One third of young people with T1D were overweight or obese. Excess weight was associated with family history (FH) of obesity for women and FH of early CVD or hypertension for men. BMI was related to decreased insulin sensitivity in both genders, but only men with T1D had metabolic impairment. Our data highlight the importance of considering family background in individuals with T1D.

4. Introdução

4.1. Prevalência e principais tipos de diabetes

O diabetes mellitus (DM) é uma doença de prevalência elevada e em ascensão no Brasil e no mundo. Segundo a 10ª edição do atlas da International Diabetes Federation (IDF) (1), o Brasil tem 15.7 milhões de pessoas com DM e é o 6º país com maior número de casos. No mundo, estima-se que sejam atualmente 537 milhões e a projeção é que esse número alcance os 783 milhões em 2045. De acordo com a IDF, as pessoas mais afetadas são as que vivem em zonas urbanas, do sexo feminino e de idade acima de 65 anos.

Identificar o tipo de DM é fundamental para designar o tratamento correto. O tipo mais comum é o diabetes mellitus tipo 2 (DM2), que corresponde a 90% dos casos e tem como principal fator desencadeante a resistência à insulina secundária ao excesso de peso e envelhecimento, tornando a reserva pancreática de insulina insuficiente para manter os níveis glicêmicos normais. Dados da pesquisa Vigitel (Vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico) do Ministério da Saúde de 2019 (Ministério da Saúde, Secretaria de Vigilância em Saúde, 2020) (2) apontam que 55.6% da população brasileira têm excesso de peso. Segundo essa mesma pesquisa, a obesidade passou de 11.8% em 2006 para 20.3% em 2019 - um aumento de 72% - enquanto o DM, no mesmo período, subiu de 5.5% para 7.4%, ou seja, o aumento da prevalência de DM acompanha a escalada dos números de excesso de peso. Esse número provavelmente é muito maior, pois segundo a IDF, um a cada dois adultos com DM não está diagnosticado (1). Um estudo recente confirmou esse achado no Brasil (3). Isso ocorre devido ao fato de o DM2 ser uma condição oligo ou assintomática em grande parte das vezes, o que ressalta a importância de fazer rotineiramente exames laboratoriais em grupos mais

suscetíveis para detectar precocemente essa doença, como é o caso das pessoas com excesso de peso.

O diabetes mellitus tipo 1 (DM1) é o segundo tipo mais prevalente e também está aumentando em incidência e prevalência no mundo (4). Segundo a IDF (1), o Brasil está em 3º lugar no número de novos casos (com 8.9 mil novos casos em crianças e adolescentes por ano) e de casos já existentes (92.3 mil casos em crianças e adolescentes por ano). Estima-se que a expectativa de vida remanescente de uma criança diagnosticada com DM1 aos 10 anos varie de 13 anos em países de baixa renda à 65 anos em países de alta renda (5). É uma doença causada por um ou mais autoanticorpos pancreáticos, como o anti-GAD (descarboxilase do ácido glutâmico), anti-IA2 (islet antigen-2 ou anti-tirosina fosfatase), anti-insulina e anti-ZnT8 (anti-transportador de zinco), desencadeados por fatores ambientais (enterovirus, fatores dietéticos, uso de antibióticos, baixa diversidade da microbiota intestinal, curta duração/ausência de amamentação) em pessoas geneticamente predispostas (variantes genéticas principalmente nos alelos HLA classe II, mas também em outros 50 genes com menor contribuição individual) (6). É possível que a autoimunidade, ao invés de ser a causa do dano celular, seja uma resposta a ela: há demonstração de que células apoptóticas podem fornecer antígenos autorreativos necessários para desencadear a autoimunidade dirigida contra células beta (7).

4.2. Resistência à insulina, obesidade e diabetes tipo 1

Sabe-se que a obesidade resulta da combinação de uma predisposição genética e fatores ambientais, especialmente sedentarismo e aumento da ingestão de calorias. Há inúmeros genes potencialmente ligados ao ganho de peso, como o *fat mass and obesity associated gene* (FTO). De contribuição maior, o estilo de vida inadequado pode advir, em pessoas com DM1, da preocupação de praticar atividade física por medo de episódios

de hipoglicemia, assim como do aumento da ingestão alimentar para evitá-los e tratá-los. A flexibilização da alimentação com a contagem de carboidratos (CHO) também poderia proporcionar maior liberdade para o consumo de alimentos mais calóricos e utilização de uma maior dose de insulina diária, o que poderia contribuir ainda mais para o ganho de peso, já que a insulina é um hormônio anabólico.

Além de ser uma possível consequência do excesso de tratamento do DM1, a obesidade também pode ser um facilitador para a instalação do DM1. Segundo a "hipótese do acelerador" (8), descrita em 2001, seriam três os fatores ligados à apoptose de células beta: constitucional (velocidade intrínseca de apoptose), resistência à insulina (pelo ganho de peso e sedentarismo, que levaria a uma piora da glicemia, à glicotoxicidade e catalisaria a apoptose) e autoimunidade (a glicotoxicidade induziria imunogenicidade contra as células beta em pessoas geneticamente predispostas). O excesso de peso, principalmente o acúmulo de gordura visceral, estaria portanto associado não apenas à falência de célula beta no DM2, mas também no DM1, sendo a diferença entre eles o tempo de evolução para a deficiência de insulina. Essa hipótese ajuda a explicar o aumento na incidência de DM1, acompanhando a elevação da prevalência de obesidade, assim como a de DM2 (9). Entre crianças e adolescentes com DM1, as com excesso de peso têm instalação da hiperglicemia em idade mais precoce, da mesma maneira que adultos com DM2 (10).

Apesar de a resistência à insulina ser habitualmente relacionada ao DM2, já está estabelecido que as pessoas com DM1, independentemente do peso e da dose de insulina, também apresentam resistência à insulina, principalmente nos tecidos periféricos (11). A ação da insulina é significativamente reduzida duas semanas após o diagnóstico, pode voltar ao normal três meses depois e contribuir para a melhora glicêmica na fase de lua de mel e, por fim, diminuir novamente em associação à piora do controle glicêmico e aumento do peso, mesmo que ainda dentro dos parâmetros normais (12). A hiperglicemia,

por si só, aumenta a resistência à insulina através da redução da captação de glicose em tecidos periféricos (13). O excesso de peso poderia agravar ainda mais essa condição de resistência à insulina e aumentar a necessidade de insulina, que por sua vez poderia aumentar peso e comorbidades associadas à obesidade, como hipertensão arterial e dislipidemia.

Além dos fatores classicamente ligados ao aumento da obesidade na população geral, como estilo de vida inadequado, o excesso de tratamento insulínico é também um fator importante para o incremento de peso em pessoas com DM1. No estudo Diabetes Control and Complication Trial (DCCT) e no seu seguimento, o estudo Epidemiology of Diabetes Interventions and Complications (EDIC), a evolução do peso das pessoas com DM1 ao longo dos anos de acordo com o tratamento recebido foi determinante para o aparecimento de comorbidades e de doença cardiovascular (DCV). Dentre os que receberam o tratamento insulínico intensivo e mantiveram uma hemoglobina glicada (HbA1c) mais próxima do ideal desde o princípio, aqueles que tiveram um ganho de peso substancial tiveram, em médio prazo, maiores níveis lipídicos e pressóricos (14) e, em longo prazo, um aumento significativo no risco de morte por DCV em relação aos que receberam o tratamento intensivo e não ganharam peso. O risco de DCV do grupo que ganhou peso com o tratamento intensivo, após 14 anos de seguimento, não foi diferente do grupo que recebeu tratamento convencional (15), isto é, o tratamento intensivo só trouxe redução de risco de morte por DCV quando não resultou em um ganho de peso desproporcional.

O DCCT (16) foi o primeiro grande estudo a demonstrar que a manutenção de uma HbA1c próxima a 7% em pessoas com DM1, obtida com um tratamento insulínico intensivo (3 a 4 aplicações de insulina e 4 glicemias capilares por dia), foi capaz de reduzir a incidência e a progressão de complicações microangiopáticas em comparação a um grupo com HbA1c mais elevada (em torno de 9%), sob tratamento convencional (1 a 2

aplicações de insulina e 1 glicemia capilar por dia). Essa vantagem em favor do grupo intensivo permaneceu no estudo EDIC, seguimento de longo prazo do DCCT, apesar da intensificação do tratamento do grupo que havia recebido inicialmente o tratamento convencional após o término do DCCT. O EDIC mostrou que mesmo 30 anos após o início do DCCT, o grupo que recebeu o tratamento intensivo desde o início, mantendo uma HbA1c mais perto da meta ideal, teve significativamente menor taxa de DCV e morte em relação ao grupo que recebeu inicialmente o tratamento convencional, depois intensificado e mantido com HbA1c semelhante ao grupo intensivo (17).

4.3. Identificação e caracterização da obesidade em pessoas com DM1

Como a DCV é a principal causa de morte tanto em pessoas com DM2 quanto nas com DM1 acima dos 30 anos (18), faz-se necessário identificar, prevenir e tratar os principais fatores de risco para a DCV. Um estudo de seguimento de uma década de uma coorte americana de cerca de 600 indivíduos com DM1 diagnosticados antes dos 18 anos, com idade média de 28 anos e duração do DM de 19 anos, apontou como principais fatores preditores de DCV a hipertensão arterial sistêmica (HAS), a dislipidemia, a doença renal crônica (DRC), a doença vascular periférica (DVP), a inflamação, o sedentarismo, a depressão e a resistência à insulina, mas não a hiperglicemia (19). Como a obesidade está associada à maior resistência à insulina, ela poderia contribuir para a elevação do risco de DCV.

O tecido adiposo é um órgão endócrino, produtor de várias substâncias conhecidas como adipocinas, como a adiponectina e a visfatina. Elas estão respectivamente inversa e diretamente associadas à piora do controle glicêmico, inflamação e morbimortalidade por DCV. A obesidade é frequentemente acompanhada por uma inflamação de baixo grau, conhecido fator ligado à patogênese do estado de resistência à insulina. Citocinas inflamatórias, como interleucina-1 (IL-1), IL-6 e TNF-alfa (fator de necrose tumoral-

alfa), seriam marcadores ligados à resistência à insulina. A neutralização de IL-1 e IL-6, mas não de TNF-alfa, mostrou-se efetiva na redução da hiperglicemia (20). Além disso, já foi demonstrado que uma endotoxemia aguda leva a um aumento da resistência à insulina em humanos através da inflamação do tecido adiposo e da modulação das vias de sinalização da insulina (21).

O método padrão ouro para estimar a resistência à insulina é o clamp euglicêmico hiperinsulinêmico. Por ser um método caro e invasivo, habitualmente se estima a resistência à insulina por um método substituto, o Homeostasis Model Assessment - Insulin Resistance (HOMA-IR), calculado a partir da relação entre glicemia e insulinemia (22). Como pessoas com DM1 não produzem insulina endógena, o HOMA-IR não poderia ser utilizado, fazendo-se então necessário um método alternativo. A partir da identificação dos principais marcadores clínicos e laboratoriais associados à resistência à insulina, foi desenvolvido o estimated Glucose Disposal Rate (eGDR), que estima a sensibilidade à insulina através de uma fórmula que inclui a relação cintura-quadril (RCQ), a presença ou não de HAS e os níveis de HbA1c, uma maneira simples, prática e com boa correlação com o clamp hiperinsulinêmico (23). Outro método alternativo é o Insulin Sensitivity prediction equation, from the Coronary Artery Calcification in Type 1 Diabetes (eIS-CACTI), uma fórmula que utiliza a medida da cintura, a dose de insulina/kg/dia, a dosagem de adiponectina, os níveis de triglicérides e a pressão arterial (PA) diastólica (24).

5. Objetivos (Artigo 1)

5.1. Geral

Identificar a prevalência e os fatores de risco associados ao sobrepeso e obesidade em indivíduos com DM1.

5.2. Específicos

5.2.1. Caracterizar os indivíduos com DM1 e sobrepeso ou obesidade em relação aos seguintes aspectos:

5.2.1.1. Distribuição de gordura (utilizando bioimpedância);

5.2.1.2. Resistência à insulina (parâmetros eGDR e do eIS-CACTI);

5.2.1.3. Comorbidades associadas à resistência à insulina, como HAS e dislipidemia;

5.2.1.4. Adipocinas (adiponectina e visfatina).

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Parents' cardiovascular risk factors are related to overweight and obesity in young Brazilians with type 1 diabetes

Fernando Valente *, Tatiana Valente, Felipe Crispim, Célia Soares Bittencourt, Valdecira Maria Piveta, Regina Celia Mello Santiago Moises, João Roberto de Sá, Sérgio Atala Dib

Diabetes Centre of Universidade Federal de São Paulo, Escola Paulista de Medicina, Brazil

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ABSTRACT

Aim: To identify family background characteristics and cardiovascular disease (CVD) risk factors linked to overweight and obesity in Brazilian with type 1 diabetes (T1D).
Methods: We performed cross-sectional anthropometric and laboratory analyses in young individuals with T1D.
Results: Among 181 participants, 87 were women and 94 were men (64%/78% normal weight, 27%/15% overweight and 9%/7% obese). Obese men were older; were more likely to be Black; had higher triglyceride levels and diastolic blood pressure (BP), lower estimated glucose disposal rate (eGDR) and higher prevalence of first-degree relatives (FDR) with hypertension and early CVD. Overweight and obese women were more likely to have lower eGDR, and obese women were more likely to have FDR with obesity.
Conclusion: One third of young people with T1D were overweight or obese. Excess weight was associated with family history (FH) of obesity for women and FH of early CVD or hypertension for men. BMI was related to decreased insulin sensitivity in both genders, but only men with T1D had metabolic impairment. Our data highlight the importance of considering family background in individuals with T1D.

1. Introduction

In recent decades, the prevalence of overweight and obesity has increased in individuals with type 1 diabetes (T1D), as well as in the general population, and these conditions are currently present in up to one third of people with T1D.[1–3] In some countries, the prevalence of overweight and obesity in women with T1D was even higher than age matched groups in the general population.[4]

Family history (FH) patterns might help to identify people with T1D with greater potential for weight gain. A previous study demonstrated that the presence of at least one relative with type 2 diabetes (T2D) was associated with weight gain in people with T1D.[5] However, the relationship between obesity and cardiovascular disease risk factors (CVDRF) in individuals with T1D remains unclear. This is an important issue, as a recent study[6] demonstrated that cardiovascular disease (CVD) is the leading cause of death in people with T1D over 30 years of age, just as it is for those with T2D.

In the Epidemiology of Diabetes Interventions and Complications (EDIC) study, people with T1D who were in the highest quartile of weight gain of the intensive glycaemic treatment group had a mortality rate similar to conventionally treated individuals after 14 years of follow-up.[7] These data remain unvalidated in other populations. In our previous study, in people with T1D lasting longer than 5 years, overweight and obesity were associated with higher prevalence of dyslipidaemia, metabolic syndrome (MS), diabetes chronic kidney disease and FH of T2D.[3] The presence of insulin resistance and MS have been associated with increased rates of complications and mortality in people with T1D.[8]

Increased (dysfunctional) adipose tissue in organs where it is not physiologically stored, such as ectopic (cardiac, pancreatic, hepatic, muscular) and abdominal fat,[9,10] known as adiposopathy, is associated with increased serum visfatin[11] and decreased adiponectin.[12] Serum visfatin are linked not only to weight gain, but also to CVD in individuals with T2D.[13] However, there are few data on such interleukins levels in people with T1D, especially in overweight or obese individuals.

Therefore, data related to the development of overweight and obesity in people with T1D and its influence in CVDRF are heteroge- neous and need to be confirmed in different populations. The present

* Corresponding author at: R. Estado de Israel, 639 V. Clementino, São Paulo, SP CEP 04022-001, Brazil.
E-mail address: fvalente.endocrino@gmail.com (F. Valente).

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study evaluates the family's clinical features and inflammatory patterns related to overweight and obesity in Brazilian young people with T1D with long disease duration.

2. Subjects and methods

2.1. Subjects

2.1.1. T1D group

A cross-sectional study was conducted in individuals with T1D aged 15 to 35 years and diagnosed between 1980 and 2010 who underwent follow-up at the Diabetes Centre of the Federal University of Sa˜o Paulo from February of 2012 to July of 2014. T1D was defined based on clinical presentation of insulinopenia (polyuria, polydipsia, weight loss, diabetic ketoacidosis (DKA), need for insulin since diagnosis), hyperglycaemia before 35 years of age with early need for insulin and/or low C-peptide and/or the presence of at least one of the islet autoantibodies (anti-GAD, anti-IA2, anti-insulin).[14] With the intention of detecting other causes, such as MODY, young people with T2D or other monogenic diabetes, other factors were also taken into account, such as family history of diabetes. Those suspected of having another type of diabetes were excluded. Exclusion criteria were hepatopathy, pneumopathy, glomerular filtration rate below 60 mL/min, chronic use of corticosteroids or any other medicine that could affect weight except for insulin and metformin. The study protocol was approved by the Ethics Committee of the Federal University of S˜ao Paulo - Escola Paulista de Medicina (UNIFESP-EPM: CEP 0653/11), and all participants signed the free informed consent form.

The individuals were divided according to gender, and each was sorted into one of three groups based on BMI status: normal weight (BMI <25 kg/m^2 in adults or below the 85th BMI percentile for <18 years), overweight (BMI between 25 and 29.9 kg/m^2 for adults or between the 85th and 94.9th percentile for <18 years) and obesity (BMI ≥ 30 kg/m^2 or percentile $\geq$95th for <18 years).

2.1.2. Control group

Sixty individuals aged 18 to 35 years without chronic diseases or a family history of diabetes mellitus and who did not use medicine that could impact their weight were recruited as control group.

2.2. Methods

2.2.1. Clinical and biochemical evaluation

Anthropometric clinical parameters such as weight, height, waist circumference and blood pressure (BP) were evaluated. A questionnaire was administered to acquire information on insulin dose (for people with T1D), demographic data, education level, ketoacidosis, smoking, date of diabetes onset, frequency of mild or moderate and severe hypoglycaemia, level of physical activity through the short International Physical Activity Questionnaire (IPAQ)[15] and FH of T1D, T2D, hypertension, dyslipidaemia, obesity and precocious CVD (before 65 years for women or 55 years for men). After the first consultation with the physician, people with T1D receive dietary guidance from a dietitian according to the ADA and Brazilian Diabetes Society guidelines. During follow-up, adherence to the diet is checked and reinforced at each appointment with the attending physician as our routine on the Diabetes Care Centre.[16,17]

A minimum of eight-hour fasting serum lipids, HbA1c and insulin dose were obtained from the latest records in the medical chart, as well as a history of microvascular complications and the use of medications among people with T1D. The presence of diabetic kidney disease was defined by elevated albuminuria levels or the use of angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker. The frequency of hypoglycaemia was self-reported considering capillary blood glucose tests below 70 mg/dL and severe hypoglycaemia in the last year. HbA1c was measured using high-performance liquid chromatography (HPLC; Tosoh G7, HLC-723; n.v. =4.0%-5.6%).

Insulin resistance in the T1D group was assessed using the estimated glucose disposal rate (eGDR) and insulin sensitivity (IS) prediction equation from the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study (eIS-CACTI). The eGDR[18] was calculated using the following equation: $24.31 - (12.2 \times \textit{waist-to-hip ratio}) - 3.29 \times \textit{HTN} - 0.57 \times \textit{HbA1c}$, considering the status of hypertension (HTN) from BP $\geq$ 140 $\times$ 90 mmHg or use of antihypertensive (0 = no; 1 = yes) and HbA1c in %. The eIS-CACTI[17] was calculated using the following formula: exp (4.06154 − 0.01317 [*waist, cm*] − 1.09615 [*insulin dose/kg*] + 0.0202 [*adiponectin, μg/mL*] − 0.00307 [*TG, mg/dL*] − 0.00733 [*Diastolic BP, mmHg*]).

For the control group, a minimum of eight-hour fasting lipids, blood glucose and insulin levels were measured. Cholesterol and triglyceride (TG) serum levels were determined using enzymatic methods (Bayer Advia 1650 analyser, serial number: CA176503-764). The samples were stored in a freezer at −70 °C until analysed.

All participants were submitted to bioimpedance analysis of body composition (Ottoboni®, InBody 230; Biospace Co, Ltd., Seoul, Korea), equipped with eight tactile electrodes,[19,20] fasting and evaluated after using the toilet.

2.2.2. Adipokine measurement

A blood sample was obtained from the T1D and control groups for the measurement of cytokines – particularly high molecular weight adiponectin (HMW adipo), which is most closely associated with insulin sensitivity and is the active form of this protein,[21] and visfatin.

Serum HMW adipo was measured using ELISA (Human High Molecular Weight Adiponectin Elisa Kit, 96-Well Plate, Cat # EZHMWA-64K, Millipore®), as well as visfatin (Visfatin C-Terminal Human, Enzyme Immunoassay Kit Protocol, Cat. No.: EK-003-80, range: 0.1–1000 ng/mL, Phoenix Pharmaceuticals®, Inc.).

2.3. Statistics

Statistical analysis was performed using the program Sigma Stat, version 3.5 (CA, USA). Fisher's exact or Chi-square test was used to verify the relationship between the qualitative variables, and the Wil- coxon test or Student *t*-test was used to compare the quantitative vari- ables in two groups, depending on the assumption of normality. The Kolmogorov–Smirnov test was used to assess normality of distribution. For comparisons between more than two groups, the Kruskal-Wallis test or ANOVA was used in case of normality assumption. In accordance with statistical methods, we needed at least 200 individuals to reach a 80% of power with an alpha of 5% and an error of 10%. Therefore, we studied a sample of 241 individuals (181 people with T1D and 60 pairs of con- trols). For statistical significance, multiple comparisons were performed in pairs. The level of significance considered was 5%.

3. Results

From 219 people with T1D evaluated, 38 were excluded because they did not meet the inclusion criteria or were suspected to have another type of diabetes. Half of them (88/173) reported DKA, 83% (60/ 72) had low or undetectable C peptide and 64% (18/28) of the in- dividuals with available information had positive pancreatic autoanti- bodies. Of the 181 participants with T1D, 52 (28.7%) were overweight or obese. Of the 94 (51.9%) who were men, 14 (14.9%) were overweight, and 7 (7.4%) were obese. Of the 87 women with T1D, 23 (26.4%) were overweight, and 8 (9.2%) were obese. Members of the control group had similar ages (23.9 ± 3.5 years), were mostly of normal weight (NW) (90%), included no obese people and were mostly women (71.7%). The clinical characteristics of the people with T1D are shown in Table 1. Obese women with T1D had significantly more first-degree relatives (FDR) with obesity and a tendency to have more HTN, whereas obese men with T1D were older and had higher frequency of

2

Table 1
Characteristics of women and men with T1D according to BMI status.

Characteristics	Total (*N* = 181)	Women with T1D (*N* = 87)				Men with T1D (*N* = 94)			
		NW (*N* = 56)	OW (*N* = 23)	OB (N = 8)	p	NW (*N* = 73)	OW (*N* = 14)	OB (N = 7)	p
Age (yr)	23.6 ± 5.5	23.8 ± 6.0	24 ± 4.0	25.4 ± 6.4	0.77	22.5 ± 5.3¥¥	23.2 ± 5.8¥	29.4 ± 3.7††§	0.01
Duration of diabetes (yr)	12.1 ± 7.2	11.8 ± 7.8	14.6 ± 6.3	12.3 ± 3.7	0.11	11.3 ± 7.1	11.4 ± 6.9	15.3 ± 8.6	0.55
White (%)	57.5	67.9	60.9	75	0.95	54.9	35.7	14.3	0.01
Mulatto (%)	30.2	19.6	26.1	12.5		36.6	57.1	28.6	
Black (%)	9.5	7.1	8.7	12.5		7.0	7.1	57.1	
Asian (%)	2.8	5.4	4.3	4.0		1.4	0	0	
Smokers (%)	6.1	3.6	4.3	12.5	0.37	9.6	0	0	0.76
HTN (%)	34.8	23.2	47.8	50	0.05	32.9	50	57.1	0.23
FH T1D (%)	13.4	16.4	13	12.5	1	12.3	7.1	16.7	0.72
FH T2D (%)	20.1	17.9	30.4	0	0.16	19.7	14.3	42.9	0.27
FH HTN (%)	60.3	62.5	73.9	62.5	0.68	50.7	57.1	100	0.03
FH dyslipidaemia (%)	36.3	33.9	47.8	25	0.45	33.8	50	28.6	0.58
FH obesity (%)	29.4	25.5	47.8	62.5	0.03	23.3	28.6	28.6	0.75
FH early CVD (%)	6.1	5.4	13	0	0.39	2.7	7.1	28.6	0.02
BMI (kg/m^2)	23.9 ± 4.2	21.8 ± 1.9	27.0 ± 1.5	34.0 ± 4.7	<0.0001	21.8 ± 1.7	27.0 ± 1.5	33.7 ± 3.3	<0.0001
Waist circumference (cm)	85.5 ± 10.6	80.2 ± 6.2§§¥¥	92.9 ± 5.5††¥¥	105.0 ± 11.7††§§	<0.0001	81.1 ± 5.3§§¥¥	92.7 ± 6.4††¥¥	111.8 ± 11.6††§§	<0.0001
Visceral fat area (cm^2)	70.7 ± 37.8	64.1 ± 23.4§§¥¥	85.4 ± 27.0††¥	147.5 ± 52.3††§	<0.0001	54.3 ± 24.9§§¥¥	81.0 ± 21.0††¥¥	139.4 ± 74.5††§§	<0.0001
Fat mass (%)	26.6 ± 10.0	30.6 ± 5.2§§¥¥	38.1 ± 4.9††¥¥	45.7 ± 4.2††§§	<0.0001	17.3 ± 4.3§§¥¥	25.4 ± 5.3††¥¥	34.8 ± 6.1††§§	<0.0001
WHR (cm/cm)	0.9 ± 0.1	0.9 ± 0.0§§¥¥	0.9 ± 0.0††¥¥	1.0 ± 0.0††§§	<0.0001	0.9 ± 0.0§§¥¥	0.9 ± 0.0††¥¥	1.0 ± 0.0††§§	<0.0001
eGDR (mg/kg/min)	7.39 ± 2.08	8 ± 2.1§§¥¥	6.1 ± 2.1††	5.4 ± 2.4††	0.0002	7.9 ± 1.7¥	6.8 ± 1.9	5.4 ± 1.9†	0.0033
eIS-CACTI	4.28 ± 2.34	4.83 ± 3.41	4.64 ± 2.2	3.65 ± 1.36	0.5245	4.16 ± 1.44	3.39 ± 1.19	2.44 ± 1.5	0.0194
SBP (mmHg)	115 ± 15	113 ± 17	113 ± 13	115 ± 14	0.8078	113 ± 13§§¥¥	126 ± 11††	134 ± 13††	<0.0001
DBP (mmHg)	74 ± 10	72 ± 12	76 ± 8	72 ± 9	0.2444	73 ± 10¥¥	79 ± 9	85 ± 8††	0.009
TC (mg/dL)	172 ± 37	177 ± 38	185 ± 43	168 ± 39	0.7024	164 ± 34	160 ± 29¥	203 ± 32§	0.0334
HDL (mg/dL)	55 ± 15	58 ± 15	58 ± 16	53 ± 13	0.5699	54 ± 14	50 ± 12	44 ± 13	0.2867
LDL (mg/dL)	98 ± 31	99 ± 30	103 ± 38	100 ± 37	0.9354	94 ± 28	95 ± 28	127 ± 42	0.2348
TG (mg/dL)	98 ± 69	104 ± 76	116 ± 73	75 ± 25	0.4475	87 ± 57¥	74 ± 34¥	180 ± 140†§	0.0279
HbA1c (mmol/mol) (%)	74 ± 21 8.9 ± 1.9	74 ± 19 8.9 ± 1.7	80 ± 31 9.5 ± 2.8	75 ± 20 9.0 ± 1.8	0.9620	73 ± 20 8.8 ± 1.8	67 ± 11 8.3 ± 1	69 ± 15 8.5 ± 1.4	0.8462
Total insulin (U/kg/d)	0.86 ± 0.27	0.9 ± 0.3	0.8 ± 0.3	0.8 ± 0.3	0.3940	0.9 ± 0.3	0.9 ± 0.3	0.7 ± 0.3	0.1143
Basal-bolus relationship	1.91 ± 1.31	1.91 ± 1.79	1.53 ± 0.83	1.47 ± 0.39	0.4105	2.08 ± 1.61	2.09 ± 1.22	1.70 ± 0.84	0.8143
HMW adipo (μg/mL)	10.4 ± 10.8	12.9 ± 13.7	16.1 ± 16.3	10.2 ± 10.7	0.4586	7.9 ± 5.2	5.2 ± 3.8	7.4 ± 4	0.1955
Visfatin (ng/mL)	2.8 ± 2.8	2.2 ± 1.5	2.3 ± 1.5	2.7 ± 1.4	0.6667	3.2 ± 3.3	4.4 ± 5.4	1.9 ± 1	0.4483

Values are given as percentage or mean ± SD. T1D, type 1 diabetes. BMI, body mass index. NW, normal weight. OW, overweight. OB, obese. FH, family history. HTN, hypertension. CVD, cardiovascular disease. WHR, waist-to-hip ratio. eGDR, estimated glucose disposal rate. eIS-CACTI, insulin sensitivity prediction equation from CACTI. SBP, systolic blood pressure. DBP, diastolic blood pressure. TC, total cholesterol. TG, triglycerides. Basal-bolus relationship: % basal/%bolus. HMW adipo, high molecular weight adiponectin. eGDR[18] was calculated using the following equation: 24.31 − (12.2 × *waist-to-hip ratio*) − 3.29 × *HTN* − 0.57 × *HbA1c*, considering the status of HTN from BP ≥ 140 × 90 mmHg or use of antihypertensive (0 = no; 1 = yes) and HbA1c in %. eIS-CACTI,[39] using the formula: exp (4.06154 − 0.01317 [*waist, cm*] − 1.09615 [*insulin dose/kg*] + 0.0202 [*adiponectin, μg/mL*] − 0.00307 [*TG, mg/dL*] − 0.00733 [*Diastolic BP, mmHg*]). *p* values according to the Kruskal-Wallis test or ANOVA for quantitatives variables and Fisher's exact or Chi-square test for qualitative variables, depending on the assumption of normality. †different from NW, §different from OW, ¥different from OB with $p < 0.05$. ††different from NW, §§different from OW, ¥¥different from OB with $p < 0.01$.

FDR with HTN or early CVD (Fig. 1). In addition, this group had a higher prevalence of Black men compared to other groups. We found no difference in duration of diabetes between groups (Table 1) or regarding self-referred hypoglycaemia (Table S1), educational level, smoking, degree of physical activity (IPAQ) and prevalence of retinopathy or albuminuria (Table S2).

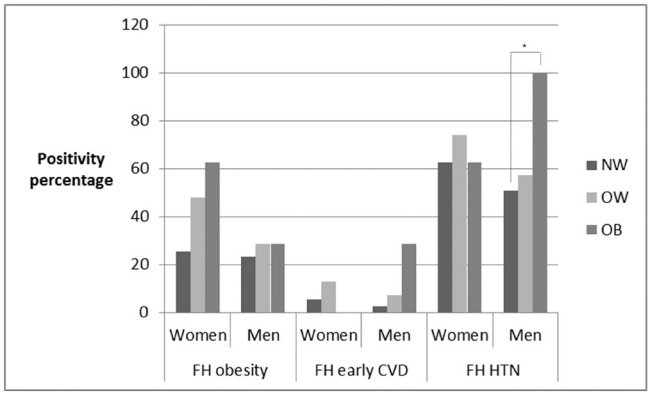

Fig. 1. Family history (FH) of obesity, early cardiovascular disease (CVD) and hypertension (HTN) in T1D group according to BMI status. Values are given as percentage. NW, normal weight. OW, overweight. OB, obese. *p < 0,05 according to the Fisher's exact or Chi-square test depending on the assumption of normality.

In addition, for both men and women, there was no statistical difference in HbA1c or in the total insulin dose/kg between the groups divided by BMI. Among women, the BMI groups differed in the same way as they did for the men regarding waist circumference, visceral fat area (VFA), body fat (BF) percentage and waist–to-hip ratio (WHR) (Table 1), with increasing values from the lowest BMI group to the highest. There was a highly significant correlation between BMI groups and VFA (r of 0.737, $p < 0.0001$).

Both overweight and obese women with T1D had higher values of skeletal lean mass (LM), fat-free mass (FFM) and lower eGDR compared to those with normal BMI (Fig. 2). Obese men with T1D had higher levels of diastolic BP, TG, total cholesterol (TC) and lower levels of eGDR and eIS-CACTI than the other groups, whereas both overweight and obese men with T1D had significantly higher systolic BP levels and higher proportions of LM and FFM (Table 1 and Fig. 3). The control group had significantly lower SBP (102.2 ± 12.3 mmHg), DBP (66.0 ± 8.3 mmHg) and higher HDL (63.6 ± 19.2 mg/dL) compared to people with T1D (Table S3). A logistic regression analysis showed that the eGDR, eIS-CACTI and SBP variables were independently related to overweight

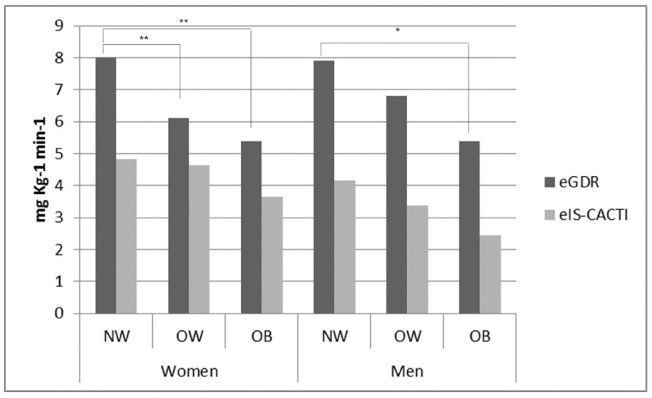

Fig. 2. Estimated glucose disposal rate (eGDR) and insulin sensitivity prediction equation from CACTI (eIS-CACTI) of individuals with T1D according to sex and BMI status. Values are given as mean. NW, normal weight. OW, overweight. OB, obese. eGDR[18] was calculated using the following equation: 24.31 − (12.2 × waist-to-hip ratio) − 3.29 × HTN − 0.57 × HbA1c, considering the status of hypertension (HTN) from BP ≥ 140 × 90 mmHg or use of antihypertensive (0 = no; 1 = yes) and HbA1c in %. eIS-CACTI,[39] using the formula: exp (4.06154 − 0.01317 [waist, cm] − 1.09615 [insulin dose/kg/day] + 0.0202 [adiponectin, μg/mL] − 0.00307 [TG, mg/dL] − 0.00733 [Diastolic BP, mmHg]). $^{**}p < 0{,}01$ and $^{*}p < 0{,}05$ according to the Wilcoxon test or Student *t*-test depending on the assumption of normality.

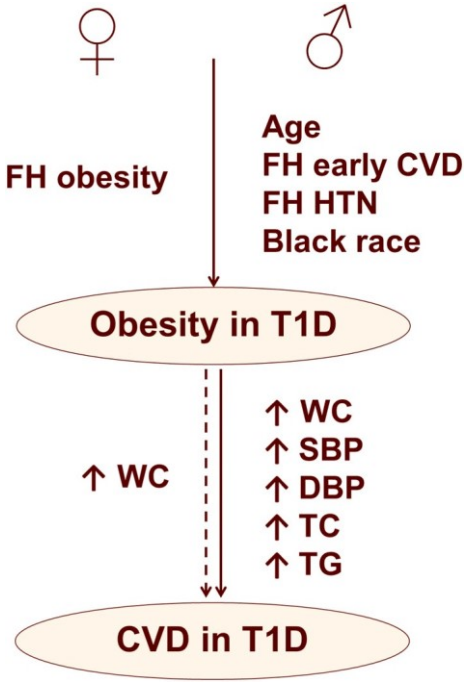

Fig. 3. Factors related to obesity in young women and men with long-duration T1D. FH, family history. CVD, cardiovascular disease. HTN, hypertension. WC, waist circumference. SBP, systolic blood pressure. DBP, diastolic blood pressure. TC, total cholesterol. TG, triglycerides.

and obesity in people with T1D.

There were no differences in HMW adipo and visfatin between the BMI groups of people with T1D (Table 1). The control group had significantly higher values of HMW adipo (15.66 ± 12.09 μg/mL) compared to NW men with T1D (7.93 ± 5.15 μg/mL) and higher visfatin levels (6.75 ± 3.69 ng/mL) versus NW women (2.17 ± 1.51 ng/mL) and NW men with T1D (3.17 ± 3.27 ng/mL).

4. Discussion

In this study, around one third of the individuals with T1D were overweight or obese. Having a FDR with obesity was a significant risk factor for women with T1D to have excess weight, whereas for men with T1D, the risk factors were having a FDR with early CVD or hypertension. Abnormal fat deposition (waist circumference, VFA and WHR) increased with BMI in both genders with T1D. BMI showed an inverse correlation with surrogate markers of insulin sensitivity (eGDR in both genders, as well as eIS-CACTI in men with T1D). Obese men with T1D had higher systemic arterial BP, serum TC and TG than did NW pairs. Visfatin levels were lower in both genders with T1D, whereas HMW adipo levels were lower only in men with T1D compared to control individuals, independent of the BMI.

The prevalence of excess weight in individuals with T1D was three times higher than in controls, especially for women. Likewise, in Australia, more than half of young adults with T1D showed the same pattern.[4] The rate of excess weight in people with T1D could be even greater worldwide, varying from 41.5% in Sweden[22] to 36 to 65% in US,[1] and reaching 46% when considered just Hispanic/Latino people with T1D.[2] In our study, Black ethnicity was an important factor linked to obesity in men, as reported in a previous study.[23]

In our study, obese men with T1D were older than NW and overweight men, which is in line with U.S. studies.[23,24] Conversely, there were no significant age differences among the groups of women. The duration of diabetes did not differ statistically between the T1D BMI groups. However, obese men were significantly older, and obese women also tended to be older, which indicates a later onset of diabetes in obese individuals. This suggests that the weight gain occurred after diabetes diagnosis and goes against the "accelerator hypothesis"[25] first described in 2001, which argues that T1D and T2D are the same disorder, but distinguishable by the measure and tempo of three accelerators, one being intrinsic and two being acquired.[26] Hence, excess weight and increased insulin resistance could accelerate beta-cell loss and decrease the age of presentation of T1D. Our findings could also indicate a less aggressive beta cell autoimmune process and, consequently, a higher endogenous insulin reserve in these individuals. A study showed a higher prevalence of CVDRF in people with idiopathic T1D compared to people with autoimmune T1D.[23] Unfortunately, we do not have enough data on serum C-peptide and anti-islet cell autoantibodies to verify this hypothesis.

In both genders, weight gain was associated with abnormal fat distribution in people with T1D, demonstrated by the significant correlation between BMI groups and VFA (r of 0.737, $p < 0.0001$). Although it is well stablished that VFA is a much better marker of insulin resistance than BMI, this finding means that in this population, the higher the BMI group, the higher the VFA. Interestingly, it was related to metabolic disorders only in men.

In a previous study of our group,[3] the overweight group had a higher prevalence of FH of T2D and of nephropathy, suggesting that insulin resistance background and the time exposed to hyperglycaemia could be factors linked to the development of MS, as previously hypothesized.[27]

Prior studies have found that FH of T2D and/or CVD is related to insulin resistance in people without diabetes[28] and to higher mortality rates in people with or without diabetes.[29] Supposing that it could have the same negative effect in people with T1D, we investigated the FH of T2D in our population. Interestingly, in our T1D group, FH of T2D (20.1%) was lower than expected, whereas FH of T1D (13.4%) was higher than usual.[27]

The distribution of eGDR values in our study in both genders was quite similar to the distribution in another study,[30] which showed an inverse relationship with the prevalence of micro and macrovascular complications in people with T1D. In addition, eGDR <8 mg kg^{-1} min^{-1} was associated with increased CVD and mortality in individuals with T1D compared to those with eGDR ≥8 and to controls. Other studies also demonstrated that low eGDR correlates better with microvascular

complications than do classic markers of insulin resistance such as WHR and daily insulin dose.[31] In our study, we found no difference in microvascular complications between BMI groups (Table S2). Ten-year follow-up data from the Pittsburgh EDC study[32] showed a high prevalence of eGDR <6.2 mg kg-1 min^{-1} in people with T1D with hard coronary artery disease (history or fatal myocardial infarction). In our data, overweight and obese women with T1D and obese men with T1D had a mean eGDR below this cut-off, indicating that those subgroups may have a higher risk of macrovascular complications and that this issue might deserve more attention.

However, the overall interpretation of these data is more complex than it seems to be. Despite the significant increase in insulin resistance in obese groups, only in men with T1D was it associated with metabolic alterations such as higher SBP and DBP, TC and TG values in relation to the other BMI groups (Fig. 3), even though all groups of women with T1D had higher BF percentage when compared to similar groups of men. Recently, a study[22] pointed out increased mortality in obese men with T1D but not in obese women with T1D compared to NW sex-matched people with T1D. However, the study did not analyse daily insulin dose, waist circumference and fat distribution. In EDIC,[7] both men and women who gained excess weight induced by intensive treatment had increased mortality more than a decade later. Therefore, although women with T1D seem to have fewer obesity related metabolic consequences, these results should be interpreted with caution, as demonstrated by double diabetes studies.[33]

Due to higher insulin resistance, a greater insulin dose/kg requirement could be expected in the obese groups.[18] However, we found no difference in the daily insulin/kg requirement between groups. Instead, we found a trend towards a lower dose of basal insulin/kg in the obese women group, which is consistent with an earlier study conducted by our research group.[3] Thus, the daily insulin requirement should be interpreted carefully as a marker of insulin resistance in T1D. A possible explanation could be variable residual endogenous insulin secretion or a lack of accuracy of the participants' reports.[33] The incidence of diabetic ketoacidosis, a marker of lower insulin reserve, did not differ between BMI status groups (Table S2).

Although adiponectin has been positively related to insulin sensitivity in T1D,[34] we found no difference in its values between BMI groups. These conflicting results could be explained by factors such as elevated HbA1c and albuminuria, which may be related to an increase in adiponectin response.[35] The role of adiponectin remains unclear; it could even be independently associated with increased all-cause and cardiovascular mortality in people with multiple conditions[36] and those with T1D.[37] On the other hand, lower visfatin levels in people with T1D compared to controls was expected.[38]

The eIS-CACTI[39] did not differ between the BMI groups of women with T1D. This might have occurred because daily doses of insulin, DBP and TG and adiponectin levels, which were factors considered in this equation, did not differ between the groups.

On the other hand, we found a decrease in eIS-CACTI in obese men with T1D in whom TG levels were higher than in NW pairs. Although the role of TG in the development of CVD remains unresolved,[40] these data indicate that high TG levels might correlate with insulin resistance, low levels of adiponectin and potential CVD risk more in men than in women with T1D in this age range.

Our study has some limitations. First, as it was a cross-sectional study, we cannot establish a cause-effect relationship between individuals' weight and the related factors. Besides, we did not use a specific questionnaire to evaluate adherence to the diet. The mean HbA1c of 8.9% (74 mmol/mol) indicates that many individuals with T1D were not meeting their glycaemic goals and were probably using lower insulin doses than necessary. The sample of people with T1D and controls with obesity was small, which could compromise the understanding of the impact of obesity in this group. Although controls were studied only for cytokine comparison, as they were volunteers, they were not strictly matched with people with T1D. The strength of our research is the validation of these metabolic variables in a sample of highly genetically diverse individuals with T1D.

5. Conclusion

In conclusion, about one third of this group of Brazilian young people with T1D was overweight or obese. Excess weight was associated with FH of obesity for women with T1D and FH of early CVD or hypertension for men with T1D. BMI was related to decreased insulin sensitivity in both genders, but only men with T1D had metabolic impairment. Therefore, our data highlight the importance of considering the family's background in the approach to individuals with T1D to avoid over- weight and obesity, the acquisition of cardiometabolic risk factors and their potential negative impact on long-term prognosis.

CRediT authorship contribution statement

Fernando Valente: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing- Original draft preparation. **Tatiana Valente**: Data curation. **Felipe Crispim**: Investigation. **Ce´lia Soares Bittencourt**: Investigation. **Valdecira Maria Piveta**: Investigation. **Regina Celia Mello Santiago Moises**: Resources. **Joa˜o Roberto de Sa´**: Writing - Review & Editing. **Se´rgio Atala Dib**: Conceptualization, Methodology, Formal analysis, Writing - Review & Editing, Supervision, Funding acquisition.

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Declaration of competing interest

Fernando Valente - Speaker of NovoNordisk, AstraZeneca and Abbott.
S´ergio Atala Dib - Board from NovoNordisk, Sanofi and Ely Lilly.
Jo˜ao Roberto de S´a - Board from NovoNordisk and Sanofi.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2021.108082.

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7. MATERIAL SUPLEMENTAR - ARTIGO 1

Table S1. Frequency of mild to moderate or severe self-referred hypoglycaemia of individuals with T1D according to sex and BMI status.

		Women with T1D (N=87)					Men with T1D (N=94)				
Characteristics		**NW (N=56)**	**OW (N=23)**	**OB (N=8)**	**Total**	**P**	**NW (N=73)**	**OW (N=14)**	**OB (N=7)**	**Total**	**p**
Severe hypoglycaemia	No	43 (76.8%)	16 (69.6%)	4 (50%)	63 (72.4%)	0.2651	59 (80.8%)	10 (71.4%)	5 (71.4%)	74 (78.7%)	0.5867
	Yes	13 (23.2%)	7 (30.4%)	4 (50%)	24 (27.6%)		14 (19.2%)	4 (28.6%)	2 (28.6%)	20 (21.3%)	
Mild/moderate hypoglycaemia	Rare	17 (30.4%)	7 (30.4%)	2 (25%)	26 (29.9%)	0.9657	31 (42.5%)	8 (57.1%)	2 (28.6%)	41 (43.6%)	0.4512
	Often	25 (44.6%)	10 (43.5%)	3 (37.5%)	38 (43.7%)		19 (26%)	3 (21.4%)	4 (57.1%)	26 (27.7%)	
	Very often	14 (25%)	6 (26.1%)	3 (37.5%)	23 (26.4%)		23 (31.5%)	3 (21.4%)	1 (14.3%)	27 (28.7%)	

Mild to moderate and severe hypoglycaemia were defined as a measurable glucose concentration < 70 mg/dL without and with altered mental and/or physical functioning that needs assistance from someone for recovery, respectively. Episodes of severe hypoglycaemia occurring in the last year were taken into account. The frequency of mild to moderate hypoglycaemia was considered uncommon, often or very often when less then weekly, once or twice a week and three times a week or more, respectively. Values are given as N (percentage). T1D, type 1 diabetes. BMI, body mass index. p values according to the Fisher's exact or Chi-square test depending on the assumption of normality.

Table S2. Educational level distribution and the prevalence of ketoacidosis, smoking, retinopathy, albuminuria and degree of physical activity (IPAQ) in participants with T1D.

Characteristics		Women with T1D (N=87) NW (N=56)	OW (N=23)	OB (N=8)	Total	P	Men with T1D (N=94) NW (N=73)	OW (N=14)	OB (N=7)	Total	p
Educational level	Elementary school	7 (12.5%)	2 (8.7%)	1 (12.5%)	10 (11.5%)	0.4716	9 (12.3%)	2 (14.3%)	1 (16.7%)	12 (12.9%)	0.2606
	Upper secondary	29 (51.8%)	10 (43.5%)	6 (75%)	45 (51.7%)		40 (54.8%)	6 (42.9%)	3 (50%)	49 (52.7%)	
	Higher education	20 (35.7%)	11 (47.8%)	1 (12.5%)	32 (36.8%)		24 (32.9%)	6 (42.9%)	2 (33.3%)	32 (34.4%)	
Ketoacidosis		32 (60.4%)	14 (63.6%)	5 (62.5%)	51 (61.4%)	1	29 (41.4%)	6 (42.9%)	2 (33.3%)	37 (41.1%)	1
Smoking	No	54 (96.4%)	22 (95.7%)	7 (87.5%)	83 (95.4%)	0.3725	66 (90.4%)	14 (100%)	7 (100%)	87 (92.6%)	0.7643
	Yes	2 (3.6%)	1 (4.3%)	1 (12.5%)	4 (4.6%)		7 (9.6%)	0 (0%)	0 (0%)	7 (7.4%)	
Retinopathy	No	41 (80.4%)	19 (82.6%)	6 (85.7%)	66 (81.5%)	1	58 (86.6%)	13 (100%)	4 (66.7%)	75 (87.2%)	0.1246
	Yes	10 (19.6%)	4 (17.4%)	1 (14.3%)	15 (18.5%)		9 (13.4%)	0 (0%)	2 (33.3%)	11 (12.8%)	
Albuminúria	No	38 (74.5%)	12 (54.5%)	4 (50%)	54 (66.7%)	0.1202	34 (49.3%)	6 (42.9%)	2 (33.3%)	42 (47.2%)	0.802
	Yes	13 (25.5%)	10 (45.5%)	4 (50%)	27 (33.3%)		35 (50.7%)	9 (57.1%)	4 (66.7%)	48 (52.8%)	
IPAQ	Sedentary	6 (10.7%)	0 (0%)	1 (12.5%)	7 (8%)	0.5878	3 (4.2%)	2 (14.3%)	0 (0%)	5 (5.4%)	0.7307
	Irreg. active	20 (35.7%)	8 (34.8%)	4 (50%)	32 (36.8%)		19 (26.4%)	4 (28.6%)	2 (28.6%)	25 (26.9%)	
	Active	27 (48.2%)	13 (56.5%)	3 (37.5%)	43 (49.4%)		40 (55.6%)	7 (50%)	5 (71.4%)	52 (55.9%)	
	Very active	3 (5.4%)	2 (8.7%)	0 (0%)	5 (5.7%)		10 (13.9%)	1 (7.1%)	0 (0%)	11 (11.8%)	

Values are given as N (percentage). Elementary school represents primary and lower secondary schooling, upper secondary means high school and higher education includes complete or incomplete university and complete or incomplete pos-graduation. T1D, type 1 diabetes. IPAQ , International Physical Activity Questionnaire. p values according to the Fisher's exact or Chi-square test depending on the assumption of normality.

Table S3. Characteristics of participants with T1D and control group.

Characteristics		People with T1D (N=129)	Controls (N=60)	p
Age (y)		23.6±5.5	23.9±3.5	0.37
Men (%)		**51.9**	**28.3**	**0.0016**
White (%)		**57.5**	**73.3**	**0.0003**
Mulatto (%)		**30.2**	**13.3**	
Black (%)		**9.5**	**1.7**	
Asian (%)		**2.8**	**11.7**	
Smokers (%)		**6.1**	**0.0**	**0.07**
HTN (%)		**34.8**	**3.3**	**0.0002**
FH T1D (%)		**13.4**	**0.0**	**0.0009**
FH T2D (%)		**20.1**	**0.0**	**<0.0001**
FH HTN (%)		60.3	45	0.05
FH Dyslipidaemia(%)		36.3	48.3	0.13
FH Obesity (%)		29.4	26.7	0.74
FH early CVD (%)		6.1	6.7	1
BMI (Kg/m²)		**23.9±4.2**	**21.9±2.3**	**0.0006**
Overweight/obese		**28.7**	**10**	**0.0084**
Waist Circumference (cm)		**85.5±10.6**	**75.9±8.2**	**<0.0001**
Visceral Fat Area (cm²)		**70.7±37.8**	**49.5±22.8**	**<0.0001**
Fat Mass (%)		26.6±10.0	24.6±6.8	0.28
WHR (cm/cm)		**0.9±0.1**	**0.8±0.0**	**0.0001**
SBP (mmHg)		**115±15**	**102±12**	**<0.0001**
DBP (mmHg)		**74±10**	**66±8**	**<0.0001**
TC (mg/dL)		172±37	176±32	0.34
HDL (mg/dL)		**55±15**	**64±19**	**0.0002**
LDL (mg/dL)		98±31	94±26	0.27
TG (mg/dL)		98±69	94±52	0.80
HMW adipo (µg/mL)		**10.35±10.79**	**15.66±12.09**	**<0.0001**
Visfatin (ng/mL)		**2.76±2.81**	**6.75±3.69**	**<0.0001**
IPAQ (%)	**Sedentary**	**6.7**	**1.7**	**<0.0001**
	Irreg. active	**31.7**	**16.7**	
	Active	**52.8**	**26.7**	
	Very active	**8.9**	**55**	

Values are given as percentage or mean ± SD. T1D, type 1 diabetes. BMI, body mass index. HTN, hypertension. FH, family history. CVD, cardiovascular disease. WHR, waist to hip ratio. SBP, systolic blood pressure. DBP, diastolic blood pressure. TC, total cholesterol. TG, triglycerides. HMW adipo, high molecular weight adiponectin. IPAQ , International Physical Activity Questionnaire. p values according to the Wilcoxon test or Student t-test for quantitatives variables and Fisher's exact or Chi-square test for qualitative variables, depending on the assumption of normality.

8. Comentários finais

Acrescentaremos entre os comentários finais considerações sobre fatores que fizerem parte também desta tese mas que ou por questão de espaço ou por considerações dos revidores não constaram da publição acima incluída, ou seja, fatores genéticos relacionados à obesidade no DM1 como o FTO e o relacionado à visfatina, a distribuição da gordura corporal e a relação da obesidade com uma das adipocinas, a visfatina.

Devido às contínuas alterações que ocorrem nas condições metabólicas do DM1 desde o seu diagnóstico, a relação entre o aumento ponderal e o risco de morte no DM1 não é linear. Alguns estudos sugerem redução do risco de morte quando ocorre ganho de peso em pessoas com DM1 (paradoxo da obesidade) e outros a associação da obesidade com aumento do risco de morte e insuficiência cardíaca após a exclusão de fatores associados à causalidade reversa (como tabagismo, fragilidade e DCV prévia), principalmente em homens (25).

No estudo Epidemiology of Diabetes Interventions and Complications (EDIC), as pessoas com DM1 tratadas intensivamente com insulina que estavam no quartil mais alto de ganho de peso tiveram uma taxa de mortalidade semelhante ao grupo tratado convencionalmente após 14 anos de acompanhamento (15). Embora a validade desses dados em outras populações ainda seja desconhecida, o aparecimento de resistência à insulina e síndrome metabólica (SM) em indivíduos com DM1 está associado a maiores taxas de complicações crônicas da doença e mortalidade (26).

Em estudo anterior do nosso grupo, a duração do DM1 foi um fator importante para o surgimento de alterações metabólicas ligadas à SM: naqueles com diagnóstico mais longo, obesidade e sobrepeso foram associados a uma maior prevalência de dislipidemia, SM, doença renal e história familiar (HF) de DM2, ainda que nos com duração menor de 5 anos, o sobrepeso ou a obesidade já tenham sido associados a níveis de HDL mais baixos em comparação aos de peso normal (27).

O excesso de peso é prevalente nos indivíduos com DM1, e mesmo entre os de Índice de Massa Corporal (IMC) normal, cerca de 20% têm excesso de gordura corporal (28). A distribuição da gordura também é relevante: o aumento do tecido adiposo (disfuncional) em órgãos onde não é armazenado fisiologicamente, como a gordura ectópica (cardíaca, pancreática, hepática, muscular) e abdominal (29, 30), conhecido como adiposopatia, está associado ao aumento da visfatina (31) e diminuição da

adiponectina (32). No entanto, existem poucos dados sobre os níveis circulantes de interleucinas nos indivíduos com DM1, especialmente naqueles com sobrepeso ou obesidade.

Além dos fatores ambientais, a presença de polimorfismos em alguns genes pode contribuir para o ganho de peso e resistência à insulina, como o gene FTO, associado a uma maior ingestão calórica (33), ou o gene da visfatina (34). Nos indivíduos com DM1, no entanto, os dados são conflitantes (35, 36). Como já se sabe, uma variante do gene da visfatina e a visfatina sérica estão ligadas não apenas ao ganho de peso, mas também à DCV em indivíduos com DM2 (37).

Desse modo, em adição aos fatores de risco discutidos no artigo 1, nesse trabalho também analisamos as adipocinas visfatina e adiponectina de alto peso molecular (*High Molecular Weight Adiponectin*, ou HMW adipo) e a herança genética (variante FTO rs9939609 e visfatina rs9770242) relacionados ao sobrepeso e à obesidade em jovens brasileiros com DM1 de longa duração. Esses dados foram comparados aos de um grupo controle de 60 estudantes de 15 a 35 anos, de duas universidades médicas de São Paulo - Universidade Federal de São Paulo - Escola Paulista de Medicina (UNIFESP-EPM) e Faculdade de Medicina do ABC, sem diabetes, sem pais diagnosticados com DM2 e sem uso de nenhum medicamento que pudesse impactar no peso.

Para isso, uma amostra de sangue foi obtida tanto do grupo com DM1 quanto do grupo controle. O DNA genômico foi extraído de leucócitos do sangue periférico usando o Puregene DNA Isolation Kit, Gentra System, EUA. Tanto a variante FTO rs9939609 quanto a visfatina rs9770242 foram genotipadas usando o TaqMan SNP probe enzyme system Genotyping Assays (Applied Byosystem, USA), de acordo com as instruções do fabricante. A HMW adipo sérica foi medida por ELISA (Human High Molecular Weight Adiponectin Elisa Kit, 96-Well Plate, Cat # EZHMWA-64K, Millipore®), bem como a visfatina (Visfatin C-Terminal Human, Enzyme Immunoassay Kit Protocol, Cat. No.: EK-003-80, range: 0.1-1000 ng/mL, Phoenix Pharmaceuticals®, Inc.).

O grupo sem diabetes tinha idade semelhante (23,9±3,5 anos) e era composto essencialmente por mulheres (71,7%) e pessoas de IMC normal (90%). O grupo controle não teve pessoas com obesidade e apresentou pressão arterial sistólica (102,2±12,3 mmHg), diastólica (66,0±8,3 mmHg) e HDL (63,6±19,2 mg/dL) significativamente menores ($p<0.005$) em relação ao grupo com DM1 e nenhuma diferença genética considerando os genes FTO e visfatina. Tiveram ainda valores significativamente mais elevados de HMW adipo em relação aos homens de peso normal com DM1 e maior

visfatina versus mulheres e homens de peso normal com DM1. Não houve diferenças em HMW adipo e visfatina entre pessoas com DM1 e IMC normal, sobrepeso ou obesidade. Os polimorfismos da visfatina e do FTO não foram associados ao excesso de peso neste grupo de indivíduos com DM1. Não houve diferença quanto à presença do alelo A do gene FTO nem do alelo T do gene da visfatina entre os grupos de pessoas com DM1 ou controle. Na literatura, polimorfismos genéticos aumentam o risco de sobrepeso e obesidade (38). Em nosso estudo, não encontramos diferenças significativas analisando a variante rs9939609, assim como outros autores (39, 40), sugerindo uma influência limitada sobre o peso, inferior aos fatores clínicos. Da mesma forma, um polimorfismo promotor do gene da visfatina rs9770242 foi relacionado à maior frequência de DCV (37), maiores valores de pressão arterial (40) e maiores níveis de insulina e glicose (34). Nossos resultados, entretanto, apontam para a falta de correlação dessas variáveis com o peso e o metabolismo da glicose, concordando com outros autores (40). Um ponto forte de nossa pesquisa que não foi contemplado no artigo 1 é a validação dessas variáveis metabólicas e avaliação desses marcadores genéticos em uma amostra de população com DM1 altamente miscigenada.

9. Resumo (Highlights)

- Um terço dos indivíduos jovens com DM1 apresentava excesso de peso e resistência à insulina
- A história familiar de obesidade foi relacionada ao excesso de peso em mulheres com DM1
- A história familiar de doença cardiovascular precoce ou hipertensão arterial sistêmica foi relacionada ao excesso de peso em homens com DM1
- O excesso de peso em pessoas com DM1 foi relacionado a fatores de risco para doença cardiovascular em homens, mas não em mulheres
- As adipocinas visfatina e adiponectina não foram relacionadas ao peso de jovens com DM1

10. Conclusões

Em conclusão, cerca de um terço do grupo de indivíduos com DM1 estudado estava com sobrepeso ou obesidade. O excesso de peso foi associado à história familiar de obesidade para mulheres com DM1 e história familiar de doença cardiovascular precoce ou hipertensão arterial sistêmica para homens com DM1, mas não com os marcadores genéticos estudados (FTO e visfatina). O IMC foi relacionado com diminuição da sensibilidade à insulina em ambos os sexos, mas apenas homens com DM1 apresentaram relação com os fatores de risco cardiometabólicos. Portanto, os resultados do nosso estudo detectaram fatores no complexo familiar que podem influenciar na resposta ponderal ao tratamento insulínico nos indivíduos com DM1 e a relação dessa com a sensibilidade à insulina e com os fatores de risco cardiometabólicos. O rastreamento e abordagem dessas variáveis durante o tratamento desses indivíduos potencialmente devem melhorar o seu prognóstico em longo prazo.

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12. Anexo I

ANEXO I- TERMO DE CONSENTIMENTO LIVRE ESCLARECIDO

Termo de Consentimento livre e Esclarecido de participação no estudo clínico sobre: OBESIDADE NO DIABETES MELLITUS DO TIPO 1: PREVALÊNCIA, DISTRIBUIÇÃO E FATORES RELACIONADOS

Nas últimas décadas tem-se detectado um aumento de obesidade na população geral incluindo as crianças e os adolescentes. Devido a isso, o perfil dos indivíduos com DM1 tem-se modificado e uma parcela destes já são obesos ao diagnóstico ou adquirem esta condição durante o tratamento. Como se sabe, a obesidade está relacionada a origem de fatores de risco cardiovasculares e modificação do prognóstico desses indivíduos.
O objetivo deste estudo é verificar a prevalência de obesidade no diabetes mellitus do tipo 1, os fatores relacionados a ela e o seu significado cardiovascular. Para isso, os participantes serão submetidos a uma avaliação de gordura corporal através de bioimpedância, que é rápido e não traz nenhum desconforto. Além disso, os participantes responderão a um questionário, de duração de 5 a 10 minutos e com 4 perguntas, para estimar o nível de atividade física. Estes dados serão correlacionados aos dados clínicos (etnia, idade, sexo, peso, altura, circunferência abdominal e do quadril e pressão arterial), laboratoriais (exames de sangue e urina) e oftalmológicos (presença de retinopatia diabética) de consultas anteriores ao longo dos anos de diabetes, com o intuito de associar características clínicas e laboratoriais com incidência de complicações crônicas do diabetes.
Este estudo poderá beneficiar o participante, já que poderá conscientizá-lo do seu percentual de gordura corpórea e correlacionar esses dados com a quantidade diária de insulina usada, alterações laboratoriais e complicações do diabetes.
Em qualquer etapa do estudo, o participante terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas. O principal investigador é a Dr. Fernando Valente, que pode ser encontrado à Rua Estado de Israel, 639, telefone 5085-0199. Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) – Rua Botucatu, 572 – 1º andar – cj 14, 5571-1062, FAX: 5539-7162 – E-mail: cepunifesp@unifesp.br
É garantida a liberdade da retirada de consentimento a qualquer momento e deixar de participar do estudo, sem qualquer prejuízo à continuidade de seu tratamento na Instituição, assim como o direito de ser mantido atualizado sobre os resultados parciais das pesquisas, quando em estudos abertos, ou de resultados que sejam do conhecimento dos pesquisadores. As informações obtidas serão analisadas em conjunto com as de outros voluntários, não sendo divulgado a identificação de nenhum paciente;
Não há despesas pessoais para o participante em qualquer fase do estudo, incluindo exames e consultas. Também não há compensação financeira relacionada à sua participação. Se existir qualquer despesa adicional, ela será absorvida pelo orçamento da pesquisa. Em caso de dano pessoal, diretamente causado pelos procedimentos ou tratamentos propostos neste estudo (nexo causal comprovado), o participante tem direito a tratamento médico na Instituição, bem como às indenizações legalmente estabelecidas. Há o compromisso do pesquisador de utilizar os dados e o material coletado somente para esta pesquisa.
Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo "**OBESIDADE NO DIABETES MELLITUS DO TIPO 1: PREVALÊNCIA, DISTRIBUIÇÃO E FATORES RELACIONADOS**".

Em resumo, o projeto tem como objetivo avaliar o excesso de peso no diabetes mellitus do tipo 1 e a sua relação com os fatores de risco cardiovasculares. Nesse sentido, utilizaremos os dados clínicos e laboratoriais presentes nas fichas de atendimento dos pacientes e a sua colaboração no

preenchimento de um questionário e da realização de um exame indolor com a duração de 1-3 minutos. Na impossibilidade de compreensão e de entendimento do jovem, o mesmo será preenchido pelos pais.

Eu discuti com o Dr. Fernando Valente sobre a minha decisão em participar nesse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas e que tenho garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

Assinatura do paciente/representante legal Data ___/___/

Data ___/___/

Assinatura da testemunha

para casos de voluntários menores de 18 anos, analfabetos, semi-analfabetos ou portadores de deficiência auditiva ou visual.

Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido deste paciente ou representante legal para a participação neste estudo.

Assinatura do responsável pelo estudo Data ___/___/

13. Anexo II

ANEXO II – PARECER CONSUBSTANCIADO DO COMITÊ DE ÉTICA EM PESQUISA DA UNIVERSIDADE FEDERAL DE SÃO PAULO/HOSPITAL SÃO PAULO

UNIFESP
UNIVERSIDADE FEDERAL DE SÃO PAULO

Universidade Federal de São Paulo
Escola Paulista de Medicina

Comitê de Ética em Pesquisa
Hospital São Paulo

São Paulo, 7 de outubro de 2011
CEP Nº: **0653/11**

Ilmo(a) Sr(a
Pesquisador(a): FERNANDO VALENTE
Disciplina/Departamento: Endocrinologia Clínica
Pesquisadores associados: Sergio Atala Dib (orientador)

Parecer Consubstanciado do Comitê de Ética em Pesquisa da Universidade Federal de São Paulo/Hospital São Paulo

TÍTULO DO ESTUDO: Obesidade no diabetes Mellitus do tipo 1: prevalência, distribuição e fatores relacionados :

CARACTERÍSTICA PRINCIPAL DO ESTUDO: Observacional

RISCOS ADICIONAIS PARA O PACIENTE: Sem risco, sem procedimento invasivo

OBJETIVO DO ESTUDO: Verificar a prevalência de obesidade, os fatores relacionados ao seu desenvolvimento e às suas carcterísticas em uma população de indivíduos com DM1

RESUMO: Estudo transversal de um grupo de indivíduos com DM1, sendo estes submetidos a uma avaliação de gordura corporal através de BIA e nível de atividade física estimado pela versão curta do IPAQ. Será feita uma reficiação retrospectiva de dados clínicos e laboratoriais de 2011 para 1990. A verificação do acúmulo de gordura será feita por aparelho de bioimpedância tetrapolar e correlacionada com o IMC ao diagnóstico e atual, duração do DM1 e dose de insulina. Serão determinados dados demográficos, laboratoriais e clínicos. Serão avaliados 250 pacientes portadores de DM1A, com diagnóstico entre 1980 e 2010, com idade mínima de 10 anos e máxima de 35 anos, atendidos no ambulatório de DM1 da Disciplina de Endocrinologia e Metabologia da UNIFESP e que ainda estejam em seguimento.

MATERIAL E MÉTODO: Estão descritos os procedimentos e os parâmetros a serem analisados.

TCLE: Adequado, contemplando a resolução 196/96

DETALHAMENTO FINANCEIRO: CAPES, PROEX - R$ 310,00

CRONOGRAMA DO ESTUDO: 18 meses

PRIMEIROS RELATÓRIOS PARCIAIS PREVISTOS PARA : 1/10/2012 e 26/9/2013

O Comitê de Ética em Pesquisa da Universidade Federal de São Paulo/Hospital São Paulo ANALISOU e APROVOU o projeto de pesquisa referenciado.
1. Comunicar toda e qualquer alteração do projeto e termo de consentimento livre e esclarecido. Nestas circunstâncias a inclusão de pacientes deve ser temporariamente interrompida até a resposta do Comitê, após análise das mudanças propostas.
2. Comunicar imediatamente ao Comitê qualquer evento adverso ocorrido durante o desenvolvimento do estudo.
3. Os dados individuais de todas as etapas da pesquisa devem ser mantidos em local seguro por 5 anos para possível auditoria dos órgãos competentes.

Atenciosamente,

Prof. Dr. José Osmar Medina Pestana
Coordenador do Comitê de Ética em Pesquisa da
Universidade Federal de São Paulo/Hospital São Paulo

14. Anexo III

ANEXO III - Nota à população

Após a descoberta da insulina, em 1921, o diabetes do tipo 1 (DM1) deixou de ser uma sentença de morte e passou a ser uma doença crônica. O aumento da longevidade das pessoas com DM1, no entanto, possibilitou o aparecimento de complicações crônicas do diabetes em vários órgãos quando a doença não é adequadamente compensada e acompanhada. A terapia com insulina, portanto, é parte fundamental para reduzir o risco dessas complicações.

Contudo, quando utilizada em doses excessivas, a insulina pode causar ganho de peso em pessoas geneticamente predispostas. Esse excesso de peso poderia aumentar a resistência à insulina, da mesma forma que o diabetes do tipo 2, e ser um fator de risco para doenças cardiovasculares como infarto do coração e derrame cerebral, as maiores causas de morte em pessoas com diabetes.

De fato, o nosso estudo, realizado no Centro de Diabetes da Universidade Federal de São Paulo, confirmou o aumento da resistência à insulina em jovens com DM1 acima do peso, e identificou alguns fatores relacionados ao ganho de peso. Em mulheres, ter pelo menos um dos pais com obesidade foi um importante fator de risco, enquanto que em homens, foram fatores de risco a idade, a etnia negra, ter pelo menos um dos pais com pressão alta ou com doença cardiovascular precoce.

Nosso estudo avaliou também algumas consequências do excesso de peso em jovens com DM1. Tanto mulheres quanto homens acima do peso tiveram um aumento da gordura na região abdominal (avaliada por bioimpedância), mas nos homens isso resultou em valores aumentados de pressão arterial, de colesterol e de triglicérides, importantes fatores de risco para doença cardiovascular. Esses dados destacam a importância de considerar a história familiar no atendimento às pessoas com DM1 para prevenir o excesso de peso e, consequentemente, doenças cardiovasculares.

15. Anexo IV- RESULTADOS COMPLETOS DA ANÁLISE ESTATÍSTICA

14.1. Comparação entre grupo controle e DM1

14.1.1 Variáveis quantitativas

Abaixo temos o descritivo das variáveis quantitativas separados pelo grupo com o p-valor da comparação entre eles.

Variável	Grupo	Média	Mediana	Desvio Padrão	Mínimo	Máximo	1º Quartil	3º Quartil	P-valor
Idade	DM1	23,55	23,00	5,51	15,00	35,00	19,00	27,00	0,3666
	Controle	23,85	23,00	3,48	19,00	34,00	22,00	25,00	
Peso	DM1	66,22	64,70	13,23	40,80	117,80	57,70	72,40	0,0144
	Controle	61,76	59,75	10,83	44,70	99,90	54,20	68,50	
Altura	DM1	166,46	166,00	8,75	147,50	193,00	160,00	172,50	0,4172
	Controle	167,50	166,25	8,00	153,50	188,00	163,25	173,00	
Índice de Massa Corporal	DM1	23,85	22,90	4,18	16,10	44,40	21,30	25,40	0,0006
	Controle	21,87	21,80	2,28	18,20	28,30	19,90	23,15	
Cintura	DM1	85,48	83,75	10,55	67,00	131,00	78,00	91,00	<0,0001
	Controle	75,87	74,75	8,21	61,00	106,00	70,75	78,75	
PAS	DM1	114,65	110,00	14,89	90,00	160,00	100,00	120,00	<0,0001
	Controle	102,24	100,00	12,25	80,00	145,00	90,00	110,00	
PAD	DM1	74,15	75,00	10,24	50,00	100,00	70,00	80,00	<0,0001
	Controle	66,03	70,00	8,31	50,00	85,00	60,00	70,00	
CT (colesterol total)	DM1	172,13	168,00	37,07	91,00	301,00	146,50	192,00	0,3351
	Controle	175,92	175,00	31,54	112,00	258,00	154,00	196,50	
HDL	DM1	54,99	54,00	14,58	25,00	100,00	45,00	63,00	0,0002
	Controle	63,55	64,00	19,19	7,00	109,00	51,00	75,00	
LDL	DM1	97,85	94,00	31,01	35,00	214,00	79,00	115,00	0,2736
	Controle	93,73	86,50	26,19	55,00	187,00	72,50	108,50	
TGC (triglicérides)	DM1	97,53	78,00	68,91	30,00	430,00	57,00	107,00	0,8001
	Controle	93,50	82,00	52,40	30,00	295,00	56,00	115,00	
Adipo HMW (ug/mL)	DM1	10,35	7,57	10,79	0,38	82,08	4,43	12,51	<0,0001
	Controle	15,66	11,43	12,09	1,95	57,29	7,72	18,13	

Variável	Grupo	Média	Mediana	Desvio Padrão	Mínimo	Máximo	1º Quartil	3º Quartil	P-valor
Visfatina (ng/mL)	DM1	2,76	2,17	2,81	0,02	24,20	1,52	3,10	<0,0001
	Controle	6,75	5,47	3,69	3,01	24,21	4,75	7,58	
Área de Gordura Visceral	DM1	70,74	65,80	37,83	14,10	298,10	47,80	84,50	<0,0001
	Controle	49,49	44,10	22,79	16,10	115,50	34,20	59,45	
Percentual de Gordura Corporal	DM1	26,62	26,10	9,95	8,90	53,00	18,30	34,50	0,2782
	Controle	24,59	25,05	6,83	6,10	39,40	20,15	28,85	
Massa Magra Esquelética	DM1	45,41	44,30	9,17	29,80	69,80	38,50	51,90	0,2772
	Controle	44,09	41,10	9,87	29,30	69,00	37,05	53,80	
Massa Livre de Gordura	DM1	48,21	47,10	9,68	31,60	74,00	40,90	55,00	0,2782
	Controle	46,82	43,80	10,40	31,30	73,40	39,40	56,95	
C/Q	DM1	0,87	0,87	0,05	0,74	1,05	0,84	0,91	0,0001
	Controle	0,84	0,84	0,04	0,76	0,94	0,81	0,87	

14.1.2. Variáveis Qualitativas

Abaixo temos as tabelas cruzadas entre as variáveis categóricas e a variável grupo.

Sexo	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
M	94	51,9%	17	28,3%	111	46,1%
F	87	48,1%	43	71,7%	130	53,9%
Total	181	100,0%	60	100,0%	241	100,0%
	p-valor =	0,0016				

IMC (0+1=NL;2+3=SP/OB)	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
0	8	4,4%	2	3,3%	10	4,1%
1	121	66,9%	52	86,7%	173	71,8%
2	37	20,4%	6	10,0%	43	17,8%
3	15	8,3%	0	0,0%	15	6,2%
Total	181	100,0%	60	100,0%	241	100,0%
	p-valor =	0,0084				

Cor (0=Branco;1=Pardo;2=Negro;3=Amarelo)	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
Branco	103	57,5%	44	73,3%	147	61,5%
Pardo	54	30,2%	8	13,3%	62	25,9%
Negro	17	9,5%	1	1,7%	18	7,5%
Amarelo	5	2,8%	7	11,7%	12	5,0%
Total	179	100,0%	60	100,0%	239	100,0%
	p-valor =	0,0003				

Fumo	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
Não	170	93,9%	60	100,0%	230	95,4%
Sim	11	6,1%	0	0,0%	11	4,6%
Total	181	100,0%	60	100,0%	241	100,0%
	p-valor =	0,0700				

AF DM1	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
Não	155	86,6%	60	100,0%	215	90,0%
Sim	24	13,4%	0	0,0%	24	10,0%
Total	179	100,0%	60	100,0%	239	100,0%
	p-valor =	0,0009				

AF DM2	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
Não	143	79,9%	60	100,0%	203	84,9%
Sim	36	20,1%	0	0,0%	36	15,1%
Total	179	100,0%	60	100,0%	239	100,0%

p-valor <	0,0001	

AF HAS	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
Não	71	39,7%	33	55,0%	104	43,5%
Sim	108	60,3%	27	45,0%	135	56,5%
Total	179	100,0%	60	100,0%	239	100,0%
p-valor =	0,0501					

AF DLP	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
Não	114	63,7%	31	51,7%	145	60,7%
Sim	65	36,3%	29	48,3%	94	39,3%
Total	179	100,0%	60	100,0%	239	100,0%
p-valor =	0,1264					

AF Obesidade	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
Não	127	70,6%	44	73,3%	171	71,3%
Sim	53	29,4%	16	26,7%	69	28,8%
Total	180	100,0%	60	100,0%	240	100,0%
p-valor =	0,7437					

AF IAM/AVC precoce	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
Não	170	93,9%	56	93,3%	226	93,8%
Sim	11	6,1%	4	6,7%	15	6,2%
Total	181	100,0%	60	100,0%	241	100,0%
p-valor =	1,0000					

HAS (0=N;1=S)	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
Não	118	65,2%	29	96,7%	147	69,7%
Sim	63	34,8%	1	3,3%	64	30,3%

Total	181	100,0%	30	100,0%	211	100,0%
	p-valor =	0,0002				

FTO rs9939609_cat	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
A/A	29	17,0%	6	10,0%	35	15,2%
A/T	83	48,5%	34	56,7%	117	50,6%
T/T	59	34,5%	20	33,3%	79	34,2%
Total	171	100,0%	60	100,0%	231	100,0%

p-valor = 0,3687

FTO_A	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
Não	59	34,5%	20	33,3%	79	34,2%
Sim	112	65,5%	40	66,7%	152	65,8%
Total	171	100,0%	60	100,0%	231	100,0%

p-valor = 1,0000

FTO_T	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
Não	29	17,0%	6	10,0%	35	15,2%
Sim	142	83,0%	54	90,0%	196	84,8%
Total	171	100,0%	60	100,0%	231	100,0%

p-valor = 0,2175

Visf rs9770242_cat	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
A/A	98	57,3%	44	73,3%	142	61,5%
A/C	61	35,7%	14	23,3%	75	32,5%
C/C	12	7,0%	2	3,3%	14	6,1%
Total	171	100,0%	60	100,0%	231	100,0%

p-valor = 0,0929

Visf_A	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
Não	12	7,0%	2	3,3%	14	6,1%
Sim	159	93,0%	58	96,7%	217	93,9%

Total	171	100,0%	60	100,0%	231	100,0%
	p-valor =	0,5290				

Visf_C	Grupo				Total	
	DM1		Controle			
	N	%	N	%	N	%
Não	98	57,3%	44	73,3%	142	61,5%
Sim	73	42,7%	16	26,7%	89	38,5%
Total	171	100,0%	60	100,0%	231	100,0%
	p-valor =	0,0313				

14.2. Analise estatística das pessoas com DM1

14.2.1. Descritivo

Variável	N	Média	Mediana	Desvio Padrão	Mínimo	Máximo	1º Quartil	3º Quartil
Idade	181	23,55	23,00	5,51	15,00	35,00	19,00	27,50
Peso	181	66,22	64,70	13,23	40,80	117,80	57,60	72,60
Altura	181	166,46	166,00	8,75	147,50	193,00	160,00	172,75
Índice de Massa Corporal	181	23,85	22,90	4,18	16,10	44,40	21,25	25,40
Cintura	180	85,48	83,75	10,55	67,00	131,00	78,00	91,00
PAS	177	114,65	110,00	14,89	90,00	160,00	100,00	120,00
PAD	177	74,15	75,00	10,24	50,00	100,00	70,00	80,00
TSH	169	2,58	2,00	2,80	0,24	30,00	1,20	3,18
CT	175	172,13	168,00	37,07	91,00	301,00	145,00	192,00
HDL	174	54,99	54,00	14,58	25,00	100,00	45,00	63,00
LDL	173	97,85	94,00	31,01	35,00	214,00	78,50	115,00
TGC	174	97,53	78,00	68,91	30,00	430,00	57,00	107,25
Adipo HMW (ug/mL)	167	10,35	7,57	10,79	0,38	82,08	4,40	12,64
Visfatina (ng/mL)	167	2,76	2,17	2,81	0,02	24,20	1,51	3,10
Área de Gordura Visceral	181	70,74	65,80	37,83	14,10	298,10	47,50	85,05
Percentual de Gordura Corporal	181	26,62	26,10	9,95	8,90	53,00	18,25	34,55
Massa Magra Esquelética	181	45,41	44,30	9,17	29,80	69,80	38,50	51,90
Massa Livre de Gordura	181	48,21	47,10	9,68	31,60	74,00	40,85	55,00
C/Q	181	0,87	0,87	0,05	0,74	1,05	0,84	0,91
Dose lenta/peso	167	0,54	0,51	0,19	0,13	1,39	0,41	0,63
Dose rápida/peso	179	0,37	0,36	0,20	0,06	1,45	0,23	0,45
Dose total insulina/peso	181	0,86	0,86	0,27	0,21	1,86	0,70	1,03
HbA1c	177	8,87	8,40	1,87	5,40	15,90	7,50	9,80
Anos de DM (inteiro)	180	12,09	12,00	7,16	0,00	32,00	6,25	16,00

eGDR	177	7,39	7,82	2,08	1,08	10,82	5,80	9,08
eIS-CACTI	159	4,28	3,97	2,34	0,50	24,69	3,06	4,96

Abaixo temos a tabela de frequência das variáveis qualitativas.

Sexo	N	%	% dos Validos
M	94	51,9	51,9
F	87	48,1	48,1
Total	181	100,0	100,0

IMC (0+1=NL;2+3=SP/OB)	N	%	% dos Validos
0	8	4,4	4,4
1	121	66,9	66,9
2	37	20,4	20,4
3	15	8,3	8,3
Total	181	100,0	100,0

Cor	N	%	% dos Validos
Branco	103	56,9	57,5
Pardo	54	29,8	30,2
Negro	17	9,4	9,5
Amarelo	5	2,8	2,8
Total	179	98,9	100,0
Em branco	2	1,1	
Total	181	100,0	

Hipoglicemias graves	N	%	% dos Validos
Não	137	75,7	75,7
Sim	44	24,3	24,3
Total	181	100,0	100,0

Hipoglicemias leves/moderadas	N	%	% dos Validos
Infrequente	67	37,0	37,0
Frequente	64	35,4	35,4
Muito Frequente	50	27,6	27,6
Total	181	100,0	100,0

Hipoglicemias leves/moderadas_2	N	%	% dos Validos
Nunca	6	3,3	3,3
1-2x/mês	61	33,7	33,7
1-2x/semana	64	35,4	35,4
3-5x/semana	38	21,0	21,0
Diariamente	12	6,6	6,6
Total	181	100,0	100,0

Fumo	N	%	% dos Validos
Não	170	93,9	93,9
Sim	11	6,1	6,1
Total	181	100,0	100,0

AF DM1	N	%	% dos Validos
Não	155	85,6	86,6
Sim	24	13,3	13,4
Total	179	98,9	100,0
Em branco	2	1,1	
Total	181	100,0	

AF DM2	N	%	% dos Validos
Não	143	79,0	79,9
Sim	36	19,9	20,1
Total	179	98,9	100,0
Em branco	2	1,1	
Total	181	100,0	

AF HAS	N	%	% dos Validos
Não	71	39,2	39,7
Sim	108	59,7	60,3
Total	179	98,9	100,0
Em branco	2	1,1	
Total	181	100,0	

AF DLP	N	%	% dos Validos
Não	114	63,0	63,7
Sim	65	35,9	36,3
Total	179	98,9	100,0
Em branco	2	1,1	
Total	181	100,0	

AF Obesidade	N	%	% dos Validos
Não	127	70,2	70,6
Sim	53	29,3	29,4
Total	180	99,4	100,0
Em branco	1	0,6	
Total	181	100,0	

AF IAM/AVC precoce	N	%	% dos Validos
Não	170	93,9	93,9
Sim	11	6,1	6,1
Total	181	100,0	100,0

HAS (0=N;1=S)	N	%	% dos Validos
Não	118	65,2	65,2
Sim	63	34,8	34,8
Total	181	100,0	100,0

FTO rs9939609_cat	N	%	% dos Validos
A/A	29	16,0	17,0
A/T	83	45,9	48,5
T/T	59	32,6	34,5
Total	171	94,5	100,0
Em branco	10	5,5	
Total	181	100,0	

FTO (A)	N	%	% dos Validos
Não	59	32,6	34,5
Sim	112	61,9	65,5
Total	171	94,5	100,0
Em branco	10	5,5	
Total	181	100,0	

FTO (T)	N	%	% dos Validos
Não	29	16,0	17,0
Sim	142	78,5	83,0
Total	171	94,5	100,0
Em branco	10	5,5	
Total	181	100,0	

Visf rs9770242_cat	N	%	% dos Validos
A/A	98	54,1	57,3
A/C	61	33,7	35,7
C/C	12	6,6	7,0
Total	171	94,5	100,0
Em branco	10	5,5	
Total	181	100,0	

Visf (A)	N	%	% dos Validos
Não	12	6,6	7,0
Sim	159	87,8	93,0
Total	171	94,5	100,0
Em branco	10	5,5	
Total	181	100,0	

Visf (C)	N	%	% dos Validos
Não	142	58,9	61,5
Sim	89	36,9	38,5
Total	231	95,9	100,0
Em branco	10	4,1	
Total	241	100,0	

14.2.2. Grupo sexo Masculino

14.2.2.1. Variáveis quantitativas

Abaixo temos o descritivo das variáveis quantitativas separados pelo grupo com o p-valor da comparação entre eles.

Variável	imc3	Média	Mediana	Desvio Padrão	Mínimo	Máximo	1º Quartil	3º Quartil	P-valor
	<=25	22,52	21,00	5,26	15,00	35,00	19,00	26,00	
Idade	25-30	23,21	21,50	5,79	15,00	33,00	20,00	28,00	**0,0097**
	30 ou +	29,43	29,00	3,74	24,00	34,00	27,00	32,50	
	<=25	81,10	81,00	5,33	71,00	92,00	77,00	85,25	
Cintura	25-30	92,68	93,00	6,37	81,00	101,00	87,00	99,00	**<0,0001**
	30 ou +	111,79	107,00	11,60	100,00	131,00	103,00	119,25	
	<=25	112,81	110,00	13,07	90,00	146,00	100,00	120,00	
PAS	25-30	126,43	127,50	10,99	110,00	150,00	120,00	130,00	**<0,0001**
	30 ou +	134,00	130,00	12,96	124,00	160,00	130,00	130,00	
	<=25	73,42	70,00	9,64	60,00	100,00	70,00	80,00	
PAD	25-30	78,93	80,00	9,24	60,00	100,00	75,00	80,00	**0,0090**
	30 ou +	85,00	80,00	8,37	80,00	100,00	80,00	90,00	
	<=25	2,62	2,13	1,96	0,42	11,40	1,31	3,35	
TSH	25-30	2,27	1,87	1,73	0,62	7,21	1,44	2,25	0,7031
	30 ou +	3,69	2,54	4,55	0,45	12,76	0,96	2,91	
	<=25	164,31	160,00	33,85	91,00	262,00	142,50	184,50	
CT	25-30	160,36	152,50	28,88	124,00	219,00	142,00	181,00	**0,0334**
	30 ou +	203,33	214,50	31,95	153,00	234,00	176,00	228,00	
	<=25	53,52	52,00	14,01	25,00	92,00	44,50	60,00	
HDL	25-30	50,14	53,00	12,38	28,00	65,00	42,00	61,00	0,2867
	30 ou +	43,83	38,50	13,08	30,00	63,00	36,00	57,00	

	<=25	93,88	92,00	28,22	43,00	199,00	75,00	109,60	
LDL	25-30	95,36	94,50	27,81	51,00	155,00	77,00	106,00	0,2348
	30 ou +	126,80	136,00	41,53	80,00	175,00	88,00	155,00	
	<=25	87,04	72,00	57,11	35,00	411,00	53,50	95,00	
TGC	25-30	74,43	62,00	34,37	38,00	155,00	50,00	101,00	**0,0279**
	30 ou +	180,33	114,00	140,20	72,00	430,00	90,00	262,00	

Variável	imc3	Média	Mediana	Desvio Padrão	Mínimo	Máximo	1º Quartil	3º Quartil	P-valor
	<=25	7,93	6,64	5,15	1,31	29,00	4,48	10,11	
Adipo HMW (ug/mL)	25-30	5,20	5,18	3,82	0,49	11,66	1,88	7,33	0,1955
	30 ou +	7,44	6,95	4,02	3,56	13,01	3,75	10,40	
	<=25	3,17	2,38	3,27	0,02	24,20	1,83	3,19	
Visfatina (ng/mL)	25-30	4,37	2,30	5,40	0,17	17,84	1,61	4,62	0,4483
	30 ou +	1,86	2,03	0,98	0,73	3,23	0,75	2,41	
	<=25	54,28	54,40	24,87	14,10	177,50	36,70	66,30	
Área de Gordura Visceral	25-30	81,02	85,00	20,96	41,30	120,60	71,00	91,70	**<0,0001**
	30 ou +	139,41	109,20	74,51	81,60	298,10	99,50	144,00	
	<=25	17,27	17,30	4,33	8,90	27,00	14,20	20,10	
Percentual de Gordura Corporal	25-30	25,40	23,35	5,33	17,30	36,20	21,40	27,40	**<0,0001**
	30 ou +	34,76	36,80	6,06	27,20	42,40	29,40	39,05	
	<=25	49,98	50,00	6,02	34,80	64,30	46,30	54,10	
Massa Magra Esquelética	25-30	57,04	56,05	6,51	48,60	69,80	52,10	58,90	**<0,0001**
	30 ou +	61,87	64,10	7,04	48,50	68,80	59,45	66,40	
	<=25	52,96	53,00	6,37	36,90	68,10	49,20	57,40	
Massa Livre de Gordura	25-30	60,51	59,40	6,96	51,60	74,00	55,30	62,40	**<0,0001**
	30 ou +	65,66	67,80	7,59	51,30	73,10	63,10	70,60	
	<=25	0,85	0,85	0,03	0,77	0,91	0,83	0,88	
C/Q	25-30	0,91	0,91	0,02	0,87	0,96	0,90	0,93	**<0,0001**
	30 ou +	0,97	0,97	0,04	0,93	1,05	0,95	0,99	
	<=25	0,57	0,54	0,21	0,23	1,39	0,43	0,63	
Dose lenta/peso	25-30	0,55	0,53	0,17	0,28	0,83	0,45	0,74	0,2155
	30 ou +	0,40	0,36	0,20	0,13	0,67	0,28	0,56	
	<=25	0,37	0,34	0,19	0,09	1,19	0,24	0,44	
Dose rápida/peso	25-30	0,33	0,38	0,15	0,06	0,62	0,22	0,42	0,2540
	30 ou +	0,27	0,25	0,14	0,14	0,55	0,17	0,29	
	<=25	0,90	0,86	0,26	0,43	1,86	0,76	1,05	
Dose total insulina/peso	25-30	0,89	0,94	0,28	0,36	1,37	0,83	1,03	0,1143
	30 ou +	0,67	0,65	0,30	0,37	1,21	0,43	0,79	

	<=25	8,76	8,30	1,77	5,50	13,50	7,60	9,90	
HbA1c	25-30	8,25	8,30	1,01	6,40	10,00	7,40	8,90	0,8462
	30 ou +	8,52	8,05	1,35	7,20	10,70	7,50	9,60	
	<=25	11,31	12,50	7,08	0,00	28,00	5,00	16,00	
Anos de DM (inteiro)	25-30	11,43	12,00	6,91	0,00	24,00	6,00	14,00	0,5497
	30 ou +	15,29	13,00	8,60	2,00	26,00	11,00	22,00	
	<=25	7,85	7,97	1,67	4,32	10,77	6,41	9,35	
eGDR	25-30	6,81	6,75	1,90	4,32	9,66	4,92	8,45	**0,0033**
	30 ou +	5,35	4,62	1,87	3,69	8,39	3,91	6,85	
	<=25	4,16	4,10	1,44	0,50	7,99	3,22	4,88	
eIS-CACTI	25-30	3,39	3,37	1,19	1,61	5,74	2,81	3,94	**0,0194**
	30 ou +	2,44	1,65	1,50	1,23	4,80	1,44	3,06	

Observamos que houve diferença estatisticamente significante nas variáveis Idade, Cintura, PAS, PAD, CT, TGC, Área de Gordura Visceral, Percentual de Gordura Corporal, Massa magra esquelética, massa livre de gordura, C/Q, eGDR e eIS-CACTI. Abaixo temos as comparações múltiplas:

Variável	Comparação	P-valor
	p(<=25 , 25-30)	0,9676
idade	p(<=25 , 30 ou +)	**0,0001**
	p(25-30 , 30 ou +)	**0,0123**
	p(<=25 , 25-30)	**<0,0001**
cintura	p(<=25 , 30 ou +)	**<0,0001**
	p(25-30 , 30 ou +)	**<0,0001**
	p(<=25 , 25-30)	**0,0003**
PAS	p(<=25 , 30 ou +)	**<0,0001**
	p(25-30 , 30 ou +)	0,3854
	p(<=25 , 25-30)	0,1462
PAD	p(<=25 , 30 ou +)	**0,0025**
	p(25-30 , 30 ou +)	0,2262
	p(<=25 , 25-30)	0,8520
CT	p(<=25 , 30 ou +)	0,0511
	p(25-30 , 30 ou +)	**0,0213**
	p(<=25 , 25-30)	0,7475
TGC	p(<=25 , 30 ou +)	**0,0234**
	p(25-30 , 30 ou +)	**0,0287**

Variável	Comparação	P-valor
Areagord	p(<=25 , 25-30)	**0,0018**
	p(<=25 , 30 ou +)	**<0,0001**
	p(25-30 , 30 ou +)	**0,0059**
percgord	p(<=25 , 25-30)	**<0,0001**
	p(<=25 , 30 ou +)	**<0,0001**
	p(25-30 , 30 ou +)	**<0,0001**
MME	p(<=25 , 25-30)	**0,0058**
	p(<=25 , 30 ou +)	**0,0083**
	p(25-30 , 30 ou +)	0,3992
MLG	p(<=25 , 25-30)	**0,0052**
	p(<=25 , 30 ou +)	**0,0121**
	p(25-30 , 30 ou +)	0,3994
CQ	p(<=25 , 25-30)	**<0,0001**
	p(<=25 , 30 ou +)	**<0,0001**
	p(25-30 , 30 ou +)	**<0,0001**
eGDR	p(<=25 , 25-30)	0,1889
	p(<=25 , 30 ou +)	**0,0321**
	p(25-30 , 30 ou +)	0,2000
eISCACTI	p(<=25 , 25-30)	0,1141
	p(<=25 , 30 ou +)	**0,0755**
	p(25-30 , 30 ou +)	0,3206

14.2.2.2. Variável qualitativa

Abaixo temos as tabelas cruzadas entre as variáveis categóricas e a variável grupo.

Cor (0=Branco;1=Pardo;2=Negro;3=Amarelo) __	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
Branco	39	54,9%	5	35,7%	1	14,3%	45	48,9%
Pardo	26	36,6%	8	57,1%	2	28,6%	36	39,1%
Negro	5	7,0%	1	7,1%	4	57,1%	10	10,9%
Amarelo	1	1,4%	0	0,0%	0	0,0%	1	1,1%
Total	71	100,0%	14	100,0%	7	100,0%	92	100,0%

p-valor =0,0136

Hipoglicemias graves	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	59	80,8%	10	71,4%	5	71,4%	74	78,7%
S	14	19,2%	4	28,6%	2	28,6%	20	21,3%
Total	73	100,0%	14	100,0%	7	100,0%	94	100,0%

p-valor =0,5867

Hipoglicemias leves/moderadas	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
Infrequente	31	42,5%	8	57,1%	2	28,6%	41	43,6%
Frequente	19	26,0%	3	21,4%	4	57,1%	26	27,7%
Muito Frequente	23	31,5%	3	21,4%	1	14,3%	27	28,7%
Total	73	100,0%	14	100,0%	7	100,0%	94	100,0%

p-valor =0,4512

Hipoglicemias leves/moderadas_2	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
Nunca	3	4,1%	2	14,3%	0	0,0%	5	5,3%
1-2x/mês	28	38,4%	6	42,9%	2	28,6%	36	38,3%
1-2x/semana	19	26,0%	3	21,4%	4	57,1%	26	27,7%
3-5x/semana	19	26,0%	3	21,4%	1	14,3%	23	24,5%
Diariamente	4	5,5%	0	0,0%	0	0,0%	4	4,3%
Total	73	100,0%	14	100,0%	7	100,0%	94	100,0%

p-valor =0,6695

Fumo	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	66	90,4%	14	100,0%	7	100,0%	87	92,6%
S	7	9,6%	0	0,0%	0	0,0%	7	7,4%
Total	73	100,0%	14	100,0%	7	100,0%	94	100,0%

p-valor =0,7643

AF DM1	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	64	87,7%	13	92,9%	5	83,3%	82	88,2%
S	9	12,3%	1	7,1%	1	16,7%	11	11,8%
Total	73	100,0%	14	100,0%	6	100,0%	93	100,0%

p-valor =0,7202

AF DM2	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	57	80,3%	12	85,7%	4	57,1%	73	79,3%
S	14	19,7%	2	14,3%	3	42,9%	19	20,7%
Total	71	100,0%	14	100,0%	7	100,0%	92	100,0%

p-valor =0,2736

AF HAS	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	35	49,3%	6	42,9%	0	0,0%	41	44,6%
S	36	50,7%	8	57,1%	7	100,0%	51	55,4%
Total	71	100,0%	14	100,0%	7	100,0%	92	100,0%

p-valor =0,0319

AF DLP	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	47	66,2%	7	50,0%	5	71,4%	59	64,1%
S	24	33,8%	7	50,0%	2	28,6%	33	35,9%
Total	71	100,0%	14	100,0%	7	100,0%	92	100,0%

p-valor =0,5845

AF Obesidade	imc3 <=25		25-30		30 ou +		Total	
	N	%	N	%	N	%	N	%
N	56	76,7%	10	71,4%	5	71,4%	71	75,5%
S	17	23,3%	4	28,6%	2	28,6%	23	24,5%
Total	73	100,0%	14	100,0%	7	100,0%	94	100,0%

p-valor =0,7541

AF IAM/AVC precoce	imc3 <=25		25-30		30 ou +		Total	
	N	%	N	%	N	%	N	%
N	71	97,3%	13	92,9%	5	71,4%	89	94,7%
S	2	2,7%	1	7,1%	2	28,6%	5	5,3%
Total	73	100,0%	14	100,0%	7	100,0%	94	100,0%

p-valor =0,0236

HAS (0=N;1=S)	imc3 <=25		25-30		30 ou +		Total	
	N	%	N	%	N	%	N	%
N	49	67,1%	7	50,0%	3	42,9%	59	62,8%
S	24	32,9%	7	50,0%	4	57,1%	35	37,2%
Total	73	100,0%	14	100,0%	7	100,0%	94	100,0%

p-valor =0,2281

FTO rs9939609_cat	imc3 <=25		25-30		30 ou +		Total	
	N	%	N	%	N	%	N	%
A/A	11	15,9%	4	30,8%	1	16,7%	16	18,2%
A/T	30	43,5%	6	46,2%	2	33,3%	38	43,2%
T/T	28	40,6%	3	23,1%	3	50,0%	34	38,6%
Total	69	100,0%	13	100,0%	6	100,0%	88	100,0%

p-valor =0,5786

FTO_A	imc3 <=25		25-30		30 ou +		Total	
	N	%	N	%	N	%	N	%
N	28	40,6%	3	23,1%	3	50,0%	34	38,6%
S	41	59,4%	10	76,9%	3	50,0%	54	61,4%

Total	69	100,0%	13	100,0%	6	100,0%	88	100,0%

p-valor =0,4004

FTO_T	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	11	15,9%	4	30,8%	1	16,7%	16	18,2%
S	58	84,1%	9	69,2%	5	83,3%	72	81,8%
Total	69	100,0%	13	100,0%	6	100,0%	88	100,0%

p-valor =0,4574

Visf rs9770242_cat ___	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
A/A	45	65,2%	7	53,8%	3	50,0%	55	62,5%
A/C	21	30,4%	4	30,8%	2	33,3%	27	30,7%
C/C	3	4,3%	2	15,4%	1	16,7%	6	6,8%
Total	69	100,0%	13	100,0%	6	100,0%	88	100,0%

p-valor =0,3135

Visf_A	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	3	4,3%	2	15,4%	1	16,7%	6	6,8%
S	66	95,7%	11	84,6%	5	83,3%	82	93,2%
Total	69	100,0%	13	100,0%	6	100,0%	88	100,0%

p-valor =0,1406

Visf_C	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	45	65,2%	7	53,8%	3	50,0%	55	62,5%
S	24	34,8%	6	46,2%	3	50,0%	33	37,5%
Total	69	100,0%	13	100,0%	6	100,0%	88	100,0%

p-valor =0,6111

14.2.3. Grupo sexo Feminino

14.2.3.1. Variáveis quantitativas

Abaixo temos o descritivo das variáveis quantitativas separados pelo grupo com o p-valor da comparação entre eles.

Variável	imc3	Média	Mediana	Desvio Padrão	Mínimo	Máximo	1º Quartil	3º Quartil	P-valor
	<=25	23,77	23,00	5,97	15,00	34,00	18,50	29,00	
Idade	25-30	24,04	24,00	3,99	15,00	31,00	21,50	27,00	0,7728
	30 ou +	25,38	26,00	6,44	16,00	34,00	20,00	30,50	
	<=25	80,16	81,00	6,15	67,00	98,00	76,00	84,00	
Cintura	25-30	92,93	94,00	5,50	80,00	101,00	91,00	95,50	**<0,0001**
	30 ou +	105,00	102,00	11,70	93,00	130,00	97,50	109,00	
	<=25	112,64	110,00	16,86	90,00	160,00	100,00	120,00	
PAS	25-30	112,87	110,00	12,56	90,00	142,00	107,00	120,00	0,8078
	30 ou +	114,75	110,00	13,85	100,00	140,00	105,00	124,00	
	<=25	72,26	70,00	11,68	50,00	100,00	60,00	80,00	
PAD	25-30	75,70	78,00	7,71	60,00	90,00	70,00	80,00	0,2444
	30 ou +	72,38	72,50	9,07	60,00	84,00	65,00	80,00	
	<=25	1,99	1,88	0,99	0,24	3,89	1,22	2,77	
TSH	25-30	3,69	2,00	6,00	0,65	30,00	1,11	3,83	0,5982
	30 ou +	2,55	2,33	1,94	0,49	6,30	0,99	3,48	
	<=25	177,26	171,00	37,77	100,00	301,00	157,00	192,00	
CT	25-30	184,74	187,00	42,98	114,00	286,00	152,50	211,00	0,7024
	30 ou +	168,38	171,00	39,41	101,00	235,00	147,50	187,00	
	<=25	58,31	57,50	14,98	28,00	100,00	48,00	66,00	
HDL	25-30	58,43	57,00	15,67	25,00	91,00	53,00	65,50	0,5699
	30 ou +	53,30	52,20	13,40	33,00	81,00	48,50	55,50	
	<=25	98,57	95,00	29,91	39,00	186,00	82,00	115,00	
LDL	25-30	102,60	92,00	37,86	46,00	214,00	78,50	123,50	0,9354
	30 ou +	100,38	96,00	36,78	35,00	163,00	90,00	116,50	
	<=25	103,98	75,50	75,27	30,00	375,00	59,50	127,50	
	25-30	115,74	95,00	72,53	40,00	334,00	58,50	149,00	
TGC	30 ou +	74,75	78,00	25,43	34,00	113,00	56,00	91,50	0,4475

Variável	imc3	Média	Mediana	Desvio Padrão	Mínimo	Máximo	1º Quartil	3º Quartil	P-valor
Adipo HMW (ug/mL)	<=25	12,86	9,54	13,65	1,70	82,08	6,30	14,70	
	25-30	16,10	10,35	16,29	0,38	55,20	4,80	22,83	0,4586
	30 ou +	10,24	6,32	10,68	1,94	28,35	2,56	16,94	
Visfatina (ng/mL)	<=25	2,17	1,91	1,51	0,80	8,27	1,25	2,38	
	25-30	2,27	1,81	1,48	0,42	5,38	1,05	3,52	0,6667
	30 ou +	2,67	2,73	1,44	0,87	4,32	1,40	3,94	
Área de Gordura Visceral	<=25	64,05	58,40	23,42	25,80	123,50	46,65	77,70	
	25-30	85,40	85,80	26,96	15,60	142,70	73,45	102,00	**<0,0001**
	30 ou +	147,46	155,85	52,27	79,60	236,00	100,90	175,30	
Percentual de Gordura Corporal	<=25	30,63	30,45	5,22	18,40	43,30	26,50	33,85	
	25-30	38,13	38,40	4,90	26,90	50,20	35,70	40,45	**<0,0001**
	30 ou +	45,69	46,15	4,20	39,80	53,00	42,30	47,90	
Massa Magra Esquelética	<=25	36,60	36,50	4,15	29,80	46,50	33,20	39,55	
	25-30	40,97	40,70	4,48	33,10	51,30	37,95	43,60	**<0,0001**
	30 ou +	43,39	41,25	4,45	39,30	50,90	40,05	47,15	
Massa Livre de Gordura	<=25	38,94	38,90	4,44	31,60	49,50	35,35	42,00	
	25-30	43,65	43,10	4,80	35,20	54,70	40,40	46,45	**<0,0001**
	30 ou +	46,03	43,75	4,71	41,70	53,80	42,45	50,15	
C/Q	<=25	0,85	0,85	0,04	0,74	0,92	0,84	0,88	
	25-30	0,92	0,91	0,03	0,85	0,97	0,91	0,94	**<0,0001**
	30 ou +	0,99	1,00	0,04	0,94	1,03	0,95	1,02	
Dose lenta/peso	<=25	0,55	0,53	0,18	0,21	1,05	0,45	0,64	
	25-30	0,48	0,47	0,15	0,15	0,78	0,39	0,60	0,0651
	30 ou +	0,43	0,44	0,05	0,34	0,49	0,40	0,47	
Dose rápida/peso	<=25	0,39	0,37	0,19	0,11	0,99	0,22	0,48	
	25-30	0,38	0,40	0,16	0,06	0,73	0,28	0,45	0,8063
	30 ou +	0,45	0,33	0,41	0,15	1,45	0,30	0,37	
Dose total insulina/peso	<=25	0,87	0,88	0,26	0,27	1,58	0,70	1,05	
	25-30	0,80	0,81	0,26	0,21	1,29	0,65	0,93	0,3940
	30 ou +	0,82	0,79	0,27	0,49	1,45	0,72	0,82	
HbA1c	<=25	8,94	8,80	1,74	6,10	13,10	7,70	9,70	
	25-30	9,49	8,70	2,78	5,40	15,90	7,50	11,30	0,9620
	30 ou +	9,03	8,85	1,81	7,40	13,10	7,75	9,25	
Anos de DM (inteiro)	<=25	11,80	11,00	7,77	0,00	32,00	6,00	16,00	
	25-30	14,61	15,00	6,28	0,00	24,00	12,50	18,50	0,1075
	30 ou +	12,25	12,00	3,73	6,00	18,00	10,50	14,50	
eGDR	<=25	8,00	8,80	2,09	2,55	10,82	6,48	9,53	
	25-30	6,13	5,68	2,12	1,08	10,23	4,84	7,75	**0,0002**
	30 ou +	5,44	5,68	2,35	1,94	7,99	3,54	7,57	
eIS-CACTI	<=25	4,83	4,41	3,41	1,70	24,69	3,35	5,22	
	25-30	4,64	4,22	2,20	1,40	8,60	2,78	6,10	0,5245
	30 ou +	3,65	3,92	1,36	1,52	5,86	2,62	4,37	

Observamos que houve diferença estatisticamente significante nas variáveis Cintura, Área de Gordura Visceral, Percentual de Gordura Corporal, Massa magra esquelética, massa livre de gordura, C/Q, e eGDR. Abaixo temos as comparações múltiplas:

Variável	Comparação	P-valor
Cintura	p(<=25 , 25-30)	**<0,0001**
	p(<=25 , 30 ou +)	**<0,0001**
	p(25-30 , 30 ou +)	**0,0046**
Areagord	p(<=25 , 25-30)	**0,0095**
	p(<=25 , 30 ou +)	**<0,0001**
	p(25-30 , 30 ou +)	**0,0141**
percgord	p(<=25 , 25-30)	**<0,0001**
	p(<=25 , 30 ou +)	**<0,0001**
	p(25-30 , 30 ou +)	**<0,0001**
MME	p(<=25 , 25-30)	**0,0009**
	p(<=25 , 30 ou +)	**<0,0001**
	p(25-30 , 30 ou +)	0,4580
MLG	p(<=25 , 25-30)	**0,0009**
	p(<=25 , 30 ou +)	**<0,0001**
	p(25-30 , 30 ou +)	0,5307
CQ	p(<=25 , 25-30)	**<0,0001**
	p(<=25 , 30 ou +)	**<0,0001**
	p(25-30 , 30 ou +)	**<0,0001**
eGDR	p(<=25 , 25-30)	**0,0031**
	p(<=25 , 30 ou +)	**0,0015**
	p(25-30 , 30 ou +)	0,7254

14.2.3.2. Variável qualitativa

Abaixo temos as tabelas cruzadas entre as variáveis categóricas e a variável grupo.

Cor (0=Branco;1=Pardo;2=Negro;3=Amarelo)	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
Branco	38	67,9%	14	60,9%	6	75,0%	58	66,7%
Pardo	11	19,6%	6	26,1%	1	12,5%	18	20,7%
Negro	4	7,1%	2	8,7%	1	12,5%	7	8,0%
Amarelo	3	5,4%	1	4,3%	0	0,0%	4	4,6%
Total	56	100,0%	23	100,0%	8	100,0%	87	100,0%

p-valor =0,9487

Hipoglicemias graves	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	43	76,8%	16	69,6%	4	50,0%	63	72,4%
S	13	23,2%	7	30,4%	4	50,0%	24	27,6%
Total	56	100,0%	23	100,0%	8	100,0%	87	100,0%

p-valor =0,2651

Hipoglicemias leves/moderadas	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
Infrequente	17	30,4%	7	30,4%	2	25,0%	26	29,9%
Frequente	25	44,6%	10	43,5%	3	37,5%	38	43,7%
Muito Frequente	14	25,0%	6	26,1%	3	37,5%	23	26,4%
Total	56	100,0%	23	100,0%	8	100,0%	87	100,0%

p-valor =0,9657

Hipoglicemias leves/moderadas_2	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
Nunca	0	0,0%	1	4,3%	0	0,0%	1	1,1%
1-2x/mês	17	30,4%	6	26,1%	2	25,0%	25	28,7%
1-2x/semana	25	44,6%	10	43,5%	3	37,5%	38	43,7%
3-5x/semana	8	14,3%	4	17,4%	3	37,5%	15	17,2%
Diariamente	6	10,7%	2	8,7%	0	0,0%	8	9,2%
Total	56	100,0%	23	100,0%	8	100,0%	87	100,0%

p-valor =0,7065

Fumo	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	54	96,4%	22	95,7%	7	87,5%	83	95,4%
S	2	3,6%	1	4,3%	1	12,5%	4	4,6%
Total	56	100,0%	23	100,0%	8	100,0%	87	100,0%

p-valor =0,3725

AF DM1	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	46	83,6%	20	87,0%	7	87,5%	73	84,9%
S	9	16,4%	3	13,0%	1	12,5%	13	15,1%
Total	55	100,0%	23	100,0%	8	100,0%	86	100,0%

p-valor =1

AF DM2	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	46	82,1%	16	69,6%	8	100,0%	70	80,5%
S	10	17,9%	7	30,4%	0	0,0%	17	19,5%
Total	56	100,0%	23	100,0%	8	100,0%	87	100,0%

p-valor =0,1638

AF HAS	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	21	37,5%	6	26,1%	3	37,5%	30	34,5%
S	35	62,5%	17	73,9%	5	62,5%	57	65,5%
Total	56	100,0%	23	100,0%	8	100,0%	87	100,0%

p-valor =0,6829

AF DLP	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	37	66,1%	12	52,2%	6	75,0%	55	63,2%
S	19	33,9%	11	47,8%	2	25,0%	32	36,8%
Total	56	100,0%	23	100,0%	8	100,0%	87	100,0%

p-valor =0,448

AF	imc3						Total	
	<=25		25-30		30 ou +			
Obesidade	N	%	N	%	N	%	N	%
N	41	74,5%	12	52,2%	3	37,5%	56	65,1%
S	14	25,5%	11	47,8%	5	62,5%	30	34,9%
Total	55	100,0%	23	100,0%	8	100,0%	86	100,0%

p-valor =0,0324

AF IAM/AVC precoce	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	53	94,6%	20	87,0%	8	100,0%	81	93,1%
S	3	5,4%	3	13,0%	0	0,0%	6	6,9%
Total	56	100,0%	23	100,0%	8	100,0%	87	100,0%

p-valor =0,3943

HAS (0=N;1=S)	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	43	76,8%	12	52,2%	4	50,0%	59	67,8%
S	13	23,2%	11	47,8%	4	50,0%	28	32,2%
Total	56	100,0%	23	100,0%	8	100,0%	87	100,0%

p-valor =0,0509

FTO rs9939609_cat	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
A/A	7	13,0%	6	28,6%	0	0,0%	13	15,7%
A/T	28	51,9%	12	57,1%	5	62,5%	45	54,2%
T/T	19	35,2%	3	14,3%	3	37,5%	25	30,1%
Total	54	100,0%	21	100,0%	8	100,0%	83	100,0%

p-valor =0,1866

FTO_A	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	19	35,2%	3	14,3%	3	37,5%	25	30,1%
S	35	64,8%	18	85,7%	5	62,5%	58	69,9%
Total	54	100,0%	21	100,0%	8	100,0%	83	100,0%

p-valor =0,1875

FTO_T	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	7	13,0%	6	28,6%	0	0,0%	13	15,7%
S	47	87,0%	15	71,4%	8	100,0%	70	84,3%
Total	54	100,0%	21	100,0%	8	100,0%	83	100,0%

p-valor =0,1221

Visf rs9770242_cat	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
A/A	28	51,9%	11	52,4%	4	50,0%	43	51,8%
A/C	21	38,9%	9	42,9%	4	50,0%	34	41,0%
C/C	5	9,3%	1	4,8%	0	0,0%	6	7,2%
Total	54	100,0%	21	100,0%	8	100,0%	83	100,0%

p-valor =0,9781

Visf_A	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	5	9,3%	1	4,8%	0	0,0%	6	7,2%
S	49	90,7%	20	95,2%	8	100,0%	77	92,8%
Total	54	100,0%	21	100,0%	8	100,0%	83	100,0%

p-valor =1

Visf_C	imc3						Total	
	<=25		25-30		30 ou +			
	N	%	N	%	N	%	N	%
N	28	51,9%	11	52,4%	4	50,0%	43	51,8%

S	26	48,1%	10	47,6%	4	50,0%	40	48,2%
Total	54	100,0%	21	100,0%	8	100,0%	83	100,0%

p-valor =1

14.3. Análise estatística citocinas

14.3.1. Correlação

14.3.1.1. Adipo HMW

14.3.1.1.1. Caso

Abaixo temos a correlação da Adipo com as demais variáveis quantitativas ou qualitativas ordinais.

	Adipo HMW (ug/mL)		
	rho	p-valor	N
Visfatina (ng/mL)	-0,0082	0,9158	167
Idade	0,1177	0,1297	167
Índice de Massa Corporal	-0,0870	0,2635	167
Cintura	-0,0285	0,7155	166
PAS	-0,0034	0,9658	163
PAD	0,1035	0,1885	163
TSH	0,0968	0,2280	157
CT	0,2633	**0,0007**	161
HDL	0,3356	**<0,0001**	160
LDL	0,1286	0,1062	159
TGC	0,0876	0,2705	160
Área de Gordura Visceral	0,0048	0,9509	167
Percentual de Gordura Corporal	0,1744	**0,0242**	167
Massa Magra Esquelética	-0,2685	**0,0005**	167
Massa Livre de Gordura	-0,2668	**0,0005**	167
C/Q	-0,1349	0,0822	167
Dose lenta/peso	-0,0388	0,6328	154
Dose rápida/peso	0,0207	0,7923	165
Dose total insulina/peso	-0,0893	0,2510	167
HbA1c	0,2073	**0,0079**	163
Anos de DM (inteiro)	0,1018	0,1918	166
eGDR	-0,1378	0,0794	163
eIS-CACTI	0,3353	**<0,0001**	159

Utilizaremos a tabela abaixo para verificar a força da correlação:

|Correlação|	Interpretação
0,00-0,20	Muito Fraca
0,20-0,40	Fraca
0,40-0,60	Moderada
0,60-0,80	Forte
0,80-1,00	Muito Forte

Assim temos que a variável Percentual de Gordura Corporal foi muito fraca e as demais variáveis foram fracas.

14.3.1.1.2. Controle

Abaixo temos a correlação da Adipo com as demais variáveis quantitativas ou qualitativas ordinais.

	Adipo HMW (ug/mL)		
	rho	p-valor	N
Visfatina (ng/mL)	-0,1152	0,3809	60
Idade	0,2400	0,0648	60
Índice de Massa Corporal	-0,2931	**0,0231**	60
Cintura	-0,2729	**0,0349**	60
PAS	-0,2029	0,1267	58
PAD	-0,1867	0,1604	58
CT	0,2655	**0,0403**	60
HDL	0,4226	**0,0008**	60
LDL	0,0441	0,7381	60
TGC	-0,0157	0,9050	60
Área de Gordura Visceral	-0,2552	**0,0491**	60
Percentual de Gordura Corporal	0,3197	**0,0128**	60
Massa Magra Esquelética	-0,2862	**0,0266**	60
Massa Livre de Gordura	-0,2791	**0,0308**	60
C/Q	-0,3395	**0,0080**	60

14.3.1.2. Visfatina

14.3.1.2.1. Caso

Abaixo temos a correlação da Visfatina com as demais variáveis quantitativas ou qualitativas ordinais.

	Visfatina (ng/mL)		
	rho	p-valor	N
Adipo HMW (ug/mL)	-0,0082	0,9158	167
Idade	-0,0581	0,4561	167
Índice de Massa Corporal	-0,0658	0,3980	167
Cintura	0,0266	0,7341	166
PAS	0,0912	0,2469	163
PAD	0,0732	0,3529	163
TSH	-0,0211	0,7926	157
CT	-0,1865	**0,0178**	161
HDL	0,0384	0,6299	160
LDL	-0,1925	**0,0151**	159
TGC	-0,1696	**0,0320**	160
Área de Gordura Visceral	-0,0466	0,5501	167
Percentual de Gordura Corporal	-0,1669	**0,0311**	167
Massa Magra Esquelética	0,1864	**0,0158**	167
Massa Livre de Gordura	0,1870	**0,0155**	167
C/Q	-0,0588	0,4504	167
Dose lenta/peso	0,1255	0,1208	154
Dose rápida/peso	-0,0703	0,3694	165
Dose total insulina/peso	0,1453	0,0609	167
HbA1c	0,0018	0,9819	163
Anos de DM (inteiro)	-0,0168	0,8298	166
eGDR	0,0838	0,2875	163
eIS-CACTI	-0,0377	0,6368	159

14.3.1.2.2. Controle

Abaixo temos a correlação da Adipo com as demais variáveis quantitativas ou qualitativas ordinais.

	Visfatina (ng/mL)		
	rho	p-valor	N
Adipo HMW (ug/mL)	-0,1152	0,3809	60
Idade	-0,1724	0,1877	60
Índice de Massa Corporal	-0,2027	0,1204	60
Cintura	-0,0284	0,8293	60
PAS	0,0044	0,9739	58
PAD	0,0555	0,6792	58
CT	0,1282	0,3291	60
HDL	0,0341	0,7961	60
LDL	0,0816	0,5355	60
TGC	-0,0169	0,8981	60
Área de Gordura Visceral	-0,0385	0,7704	60
Percentual de Gordura Corporal	-0,0658	0,6172	60
Massa Magra Esquelética	-0,1065	0,4182	60
Massa Livre de Gordura	-0,1090	0,4071	60
C/Q	-0,1722	0,1883	60

14.3.2. Variáveis Qualitativas

14.3.2.1. Adipo HMW

14.3.2.1.1. Caso

Abaixo temos as tabelas cruzadas entre as variáveis categóricas e a variável grupo.

Sexo (0=M, 1=F)	adipo_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
M	24	57,1%	28	66,7%	24	57,1%	10	24,4%	86	51,5%
F	18	42,9%	14	33,3%	18	42,9%	31	75,6%	81	48,5%
Total	42	100,0%	42	100,0%	42	100,0%	41	100,0%	167	100,0%
	p-valor	**=0,0011**								

Cor (0=Branco;1=Pardo;2=Negro;3=Amarelo)	adipo_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
Branco	18	43,9%	25	59,5%	27	65,9%	27	65,9%	97	58,8%
Pardo	16	39,0%	11	26,2%	13	31,7%	9	22,0%	49	29,7%
Negro	4	9,8%	6	14,3%	0	0,0%	5	12,2%	15	9,1%
Amarelo	3	7,3%	0	0,0%	1	2,4%	0	0,0%	4	2,4%
Total	41	100,0%	42	100,0%	41	100,0%	41	100,0%	165	100,0%

p-valor = 0,0417

Hipoglicemias graves	adipo_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	30	71,4%	33	78,6%	36	85,7%	28	68,3%	127	76,0%
S	12	28,6%	9	21,4%	6	14,3%	13	31,7%	40	24,0%
Total	42	100,0%	42	100,0%	42	100,0%	41	100,0%	167	100,0%

p-valor =0,2366

Hipoglicemias leves/moderadas	adipo_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
Infrequente	14	33,3%	18	42,9%	18	42,9%	12	29,3%	62	37,1%
Frequente	17	40,5%	14	33,3%	9	21,4%	18	43,9%	58	34,7%
Muito frequente	11	26,2%	10	23,8%	15	35,7%	11	26,8%	47	28,1%
Total	42	100,0%	42	100,0%	42	100,0%	41	100,0%	167	100,0%

p-valor =0,374

Hipoglicemias leves/moderadas_2	adipo_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
Nunca	2	4,8%	2	4,8%	1	2,4%	0	0,0%	5	3,0%
1-2x/mês	12	28,6%	16	38,1%	17	40,5%	12	29,3%	57	34,1%
1-2x/semana	17	40,5%	14	33,3%	9	21,4%	18	43,9%	58	34,7%
3-5x/semana	9	21,4%	8	19,0%	13	31,0%	7	17,1%	37	22,2%
Diariamente	2	4,8%	2	4,8%	2	4,8%	4	9,8%	10	6,0%
Total	42	100,0%	42	100,0%	42	100,0%	41	100,0%	167	100,0%

p-valor =0,5571

Fumo	adipo_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	41	97,6%	38	90,5%	41	97,6%	39	95,1%	159	95,2%
S	1	2,4%	4	9,5%	1	2,4%	2	4,9%	8	4,8%
Total	42	100,0%	42	100,0%	42	100,0%	41	100,0%	167	100,0%

p-valor =0,4511

AF DM1	adipo_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	36	85,7%	38	90,5%	37	88,1%	35	87,5%	146	88,0%
S	6	14,3%	4	9,5%	5	11,9%	5	12,5%	20	12,0%
Total	42	100,0%	42	100,0%	42	100,0%	40	100,0%	166	100,0%

p-valor =0,9542

AF DM2	adipo_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	35	83,3%	35	83,3%	33	80,5%	31	77,5%	134	81,2%
S	7	16,7%	7	16,7%	8	19,5%	9	22,5%	31	18,8%
Total	42	100,0%	42	100,0%	41	100,0%	40	100,0%	165	100,0%

p-valor =0,8873

AF HAS	adipo_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	16	38,1%	21	51,2%	17	40,5%	12	30,0%	66	40,0%
S	26	61,9%	20	48,8%	25	59,5%	28	70,0%	99	60,0%
Total	42	100,0%	41	100,0%	42	100,0%	40	100,0%	165	100,0%

p-valor =0,2752

AF DLP	adipo_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	27	64,3%	27	67,5%	25	59,5%	26	63,4%	105	63,6%
S	15	35,7%	13	32,5%	17	40,5%	15	36,6%	60	36,4%
Total	42	100,0%	40	100,0%	42	100,0%	41	100,0%	165	100,0%

p-valor =0,9102

AF Obesidade	adipo_q_caso								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
0	34	81,0%	24	57,1%	32	76,2%	26	65,0%	116	69,9%
1	8	19,0%	18	42,9%	10	23,8%	14	35,0%	50	30,1%
Total	42	100,0%	42	100,0%	42	100,0%	40	100,0%	166	100,0%
	p-valor =0,0784									

AF IAM/AVC precoce	adipo_q_caso								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	40	95,2%	40	95,2%	40	95,2%	38	92,7%	158	94,6%
S	2	4,8%	2	4,8%	2	4,8%	3	7,3%	9	5,4%
Total	42	100,0%	42	100,0%	42	100,0%	41	100,0%	167	100,0%
	p-valor =0,9093									

HAS (0=N;1=S)	adipo_q_caso								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	29	69,0%	29	69,0%	31	73,8%	21	51,2%	110	65,9%
S	13	31,0%	13	31,0%	11	26,2%	20	48,8%	57	34,1%
Total	42	100,0%	42	100,0%	42	100,0%	41	100,0%	167	100,0%
	p-valor =0,1511									

FTO rs9939609_cat	adipo_q_caso								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
A/A	5	11,9%	7	16,7%	8	19,0%	8	19,5%	28	16,8%
A/T	19	45,2%	26	61,9%	18	42,9%	18	43,9%	81	48,5%
T/T	18	42,9%	9	21,4%	16	38,1%	15	36,6%	58	34,7%
Total	42	100,0%	42	100,0%	42	100,0%	41	100,0%	167	100,0%
	p-valor =0,3895									

FTO_A	adipo_q_caso								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	18	42,9%	9	21,4%	16	38,1%	15	36,6%	58	34,7%
S	24	57,1%	33	78,6%	26	61,9%	26	63,4%	109	65,3%
Total	42	100,0%	42	100,0%	42	100,0%	41	100,0%	167	100,0%
	p-valor =0,1723									

FTO_T	adipo_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	5	11,9%	7	16,7%	8	19,0%	8	19,5%	28	16,8%
S	37	88,1%	35	83,3%	34	81,0%	33	80,5%	139	83,2%
Total	42	100,0%	42	100,0%	42	100,0%	41	100,0%	167	100,0%
	p-valor	=0,7679								

Visf rs9770242_cat	adipo_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
A/A	25	59,5%	22	52,4%	27	64,3%	21	51,2%	95	56,9%
A/C	14	33,3%	17	40,5%	14	33,3%	15	36,6%	60	35,9%
C/C	3	7,1%	3	7,1%	1	2,4%	5	12,2%	12	7,2%
Total	42	100,0%	42	100,0%	42	100,0%	41	100,0%	167	100,0%
	p-valor	=0,6871								

Visf_A	adipo_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	3	7,1%	3	7,1%	1	2,4%	5	12,2%	12	7,2%
S	39	92,9%	39	92,9%	41	97,6%	36	87,8%	155	92,8%
Total	42	100,0%	42	100,0%	42	100,0%	41	100,0%	167	100,0%
	p-valor	=0,3845								

Visf_C	adipo_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	25	59,5%	22	52,4%	27	64,3%	21	51,2%	95	56,9%
S	17	40,5%	20	47,6%	15	35,7%	20	48,8%	72	43,1%
Total	42	100,0%	42	100,0%	42	100,0%	41	100,0%	167	100,0%
	p-valor	=0,5963								

14.3.2.1.2. Controle

Sexo (0=M, 1=F)	adipo_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
M	9	60,0%	5	33,3%	2	13,3%	1	6,7%	17	28,3%
F	6	40,0%	10	66,7%	13	86,7%	14	93,3%	43	71,7%
Total	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%
	p-valor	**=0,0062**								

Cor (0=Branco;1=Pardo;2=Negro;3=Amarelo)	adipo_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
Branco	11	73,3%	9	60,0%	11	73,3%	13	86,7%	44	73,3%
Pardo	2	13,3%	1	6,7%	3	20,0%	2	13,3%	8	13,3%
Negro	0	0,0%	1	6,7%	0	0,0%	0	0,0%	1	1,7%
Amarelo	2	13,3%	4	26,7%	1	6,7%	0	0,0%	7	11,7%
Total	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,4145

Fumo	adipo_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%
Total	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%

AF DM1	adipo_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%
Total	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%

AF DM2	adipo_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%
Total	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%

AF HAS	adipo_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	8	53,3%	8	53,3%	10	66,7%	7	46,7%	33	55,0%
S	7	46,7%	7	46,7%	5	33,3%	8	53,3%	27	45,0%
Total	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,8002

AF DLP	adipo_q_contr	Total

	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	7	46,7%	10	66,7%	8	53,3%	6	40,0%	31	51,7%
S	8	53,3%	5	33,3%	7	46,7%	9	60,0%	29	48,3%
Total	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,5765

AF Obesidade	adipo_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	12	80,0%	12	80,0%	9	60,0%	11	73,3%	44	73,3%
S	3	20,0%	3	20,0%	6	40,0%	4	26,7%	16	26,7%
Total	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,7056

AF IAM/AVC precoce	adipo_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	15	100,0%	13	86,7%	14	93,3%	14	93,3%	56	93,3%
S	0	0,0%	2	13,3%	1	6,7%	1	6,7%	4	6,7%
Total	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,9012

HAS (0=N;1=S)	adipo_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	6	85,7%	4	100,0%	10	100,0%	9	100,0%	29	96,7%
S	1	14,3%	0	0,0%	0	0,0%	0	0,0%	1	3,3%
Total	7	100,0%	4	100,0%	10	100,0%	9	100,0%	30	100,0%

p-valor =0,3717

FTO rs9939609_cat	adipo_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
A/A	1	6,7%	2	13,3%	1	6,7%	2	13,3%	6	10,0%
A/T	11	73,3%	8	53,3%	6	40,0%	9	60,0%	34	56,7%
T/T	3	20,0%	5	33,3%	8	53,3%	4	26,7%	20	33,3%
Total	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,5582

FTO_A	adipo_q_contr								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	3	20,0%	5	33,3%	8	53,3%	4	26,7%	20	33,3%
S	12	80,0%	10	66,7%	7	46,7%	11	73,3%	40	66,7%
Total	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,3231

FTO_T	adipo_q_contr								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	1	6,7%	2	13,3%	1	6,7%	2	13,3%	6	10,0%
S	14	93,3%	13	86,7%	14	93,3%	13	86,7%	54	90,0%
Total	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =1

Visf rs9770242_cat	adipo_q_contr								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
A/A	9	60,0%	13	86,7%	11	73,3%	11	73,3%	44	73,3%
A/C	5	33,3%	2	13,3%	4	26,7%	3	20,0%	14	23,3%
C/C	1	6,7%	0	0,0%	0	0,0%	1	6,7%	2	3,3%
Total	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,6443

Visf_A	adipo_q_contr								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	1	6,7%	0	0,0%	0	0,0%	1	6,7%	2	3,3%
S	14	93,3%	15	100,0%	15	100,0%	14	93,3%	58	96,7%
Total	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =1

Visf_C	adipo_q_contr								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	9	60,0%	13	86,7%	11	73,3%	11	73,3%	44	73,3%
S	6	40,0%	2	13,3%	4	26,7%	4	26,7%	16	26,7%
Total	15	100,0%	15	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,4873

14.3.2.2. Visfatina

14.3.2.2.1. Caso

Abaixo temos as tabelas cruzadas entre as variáveis categóricas e a variável grupo.

Sexo (0=M, 1=F)	visf_q_caso								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
M	15	35,7%	21	48,8%	25	59,5%	25	62,5%	86	51,5%
F	27	64,3%	22	51,2%	17	40,5%	15	37,5%	81	48,5%
Total	42	100,0%	43	100,0%	42	100,0%	40	100,0%	167	100,0%

p-valor =0,0611

Cor (0=Branco;1=Pardo;2=Negro;3=Amarelo)	visf_q_caso								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
Branco	26	61,9%	23	56,1%	22	52,4%	26	65,0%	97	58,8%
Pardo	10	23,8%	16	39,0%	13	31,0%	10	25,0%	49	29,7%
Negro	5	11,9%	1	2,4%	5	11,9%	4	10,0%	15	9,1%
Amarelo	1	2,4%	1	2,4%	2	4,8%	0	0,0%	4	2,4%
Total	42	100,0%	41	100,0%	42	100,0%	40	100,0%	165	100,0%

p-valor =0,5501

Hipoglicemias graves	visf_q_caso								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	34	81,0%	31	72,1%	33	78,6%	29	72,5%	127	76,0%
S	8	19,0%	12	27,9%	9	21,4%	11	27,5%	40	24,0%
Total	42	100,0%	43	100,0%	42	100,0%	40	100,0%	167	100,0%

p-valor =0,7328

Hipoglicemias leves/moderadas	visf_q_caso								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
Infrequente	14	33,3%	16	37,2%	16	38,1%	16	40,0%	62	37,1%
Frequente	12	28,6%	14	32,6%	15	35,7%	17	42,5%	58	34,7%
Muito frequente	16	38,1%	13	30,2%	11	26,2%	7	17,5%	47	28,1%
Total	42	100,0%	43	100,0%	42	100,0%	40	100,0%	167	100,0%

p-valor =0,5841

Hipoglicemias leves/moderadas_2	visf_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
Nunca	2	4,8%	0	0,0%	2	4,8%	1	2,5%	5	3,0%
1-2x/mês	12	28,6%	16	37,2%	14	33,3%	15	37,5%	57	34,1%
1-2x/semana	12	28,6%	14	32,6%	15	35,7%	17	42,5%	58	34,7%
3-5x/semana	11	26,2%	11	25,6%	10	23,8%	5	12,5%	37	22,2%
Diariamente	5	11,9%	2	4,7%	1	2,4%	2	5,0%	10	6,0%
Total	42	100,0%	43	100,0%	42	100,0%	40	100,0%	167	100,0%

p-valor =0,6492

Fumo	visf_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	40	95,2%	40	93,0%	40	95,2%	39	97,5%	159	95,2%
S	2	4,8%	3	7,0%	2	4,8%	1	2,5%	8	4,8%
Total	42	100,0%	43	100,0%	42	100,0%	40	100,0%	167	100,0%

p-valor =0,9607

AF DM1	visf_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	38	92,7%	33	76,7%	39	92,9%	36	90,0%	146	88,0%
S	3	7,3%	10	23,3%	3	7,1%	4	10,0%	20	12,0%
Total	41	100,0%	43	100,0%	42	100,0%	40	100,0%	166	100,0%

p-valor =0,1106

AF DM2	visf_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	35	83,3%	35	85,4%	30	71,4%	34	85,0%	134	81,2%
S	7	16,7%	6	14,6%	12	28,6%	6	15,0%	31	18,8%
Total	42	100,0%	41	100,0%	42	100,0%	40	100,0%	165	100,0%

p-valor =0,3612

AF HAS	visf_q_caso								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	17	41,5%	16	38,1%	19	45,2%	14	35,0%	66	40,0%
S	24	58,5%	26	61,9%	23	54,8%	26	65,0%	99	60,0%
Total	41	100,0%	42	100,0%	42	100,0%	40	100,0%	165	100,0%

p-valor =0,814

AF DLP	visf_q_caso								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	26	63,4%	25	58,1%	28	68,3%	26	65,0%	105	63,6%
S	15	36,6%	18	41,9%	13	31,7%	14	35,0%	60	36,4%
Total	41	100,0%	43	100,0%	41	100,0%	40	100,0%	165	100,0%

p-valor =0,8117

AF Obesidade	visf_q_caso								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	23	56,1%	31	72,1%	36	85,7%	26	65,0%	116	69,9%
S	18	43,9%	12	27,9%	6	14,3%	14	35,0%	50	30,1%
Total	41	100,0%	43	100,0%	42	100,0%	40	100,0%	166	100,0%

p-valor =0,0223

AF IAM/AVC precoce	visf_q_caso								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	38	90,5%	41	95,3%	42	100,0%	37	92,5%	158	94,6%
S	4	9,5%	2	4,7%	0	0,0%	3	7,5%	9	5,4%
Total	42	100,0%	43	100,0%	42	100,0%	40	100,0%	167	100,0%

p-valor =0,1815

HAS (0=N;1=S)	visf_q_caso								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	24	57,1%	28	65,1%	31	73,8%	27	67,5%	110	65,9%
S	18	42,9%	15	34,9%	11	26,2%	13	32,5%	57	34,1%
Total	42	100,0%	43	100,0%	42	100,0%	40	100,0%	167	100,0%

p-valor =0,461

FTO rs9939609_cat	visf_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
A/A	7	16,7%	8	18,6%	7	16,7%	6	15,0%	28	16,8%
A/T	25	59,5%	14	32,6%	23	54,8%	19	47,5%	81	48,5%
T/T	10	23,8%	21	48,8%	12	28,6%	15	37,5%	58	34,7%
Total	42	100,0%	43	100,0%	42	100,0%	40	100,0%	167	100,0%

p-valor =0,212

FTO_A	visf_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	10	23,8%	21	48,8%	12	28,6%	15	37,5%	58	34,7%
S	32	76,2%	22	51,2%	30	71,4%	25	62,5%	109	65,3%
Total	42	100,0%	43	100,0%	42	100,0%	40	100,0%	167	100,0%

p-valor =0,0837

FTO_T	visf_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	7	16,7%	8	18,6%	7	16,7%	6	15,0%	28	16,8%
S	35	83,3%	35	81,4%	35	83,3%	34	85,0%	139	83,2%
Total	42	100,0%	43	100,0%	42	100,0%	40	100,0%	167	100,0%

p-valor =0,9929

Visf rs9770242_cat	visf_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
A/A	23	54,8%	24	55,8%	25	59,5%	23	57,5%	95	56,9%
A/C	15	35,7%	17	39,5%	13	31,0%	15	37,5%	60	35,9%
C/C	4	9,5%	2	4,7%	4	9,5%	2	5,0%	12	7,2%
Total	42	100,0%	43	100,0%	42	100,0%	40	100,0%	167	100,0%

p-valor =0,939

Visf_A	visf_q_caso									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	4	9,5%	2	4,7%	4	9,5%	2	5,0%	12	7,2%
S	38	90,5%	41	95,3%	38	90,5%	38	95,0%	155	92,8%
Total	42	100,0%	43	100,0%	42	100,0%	40	100,0%	167	100,0%

p-valor =0,7322

Visf_C	visf_q_caso								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	23	54,8%	24	55,8%	25	59,5%	23	57,5%	95	56,9%
S	19	45,2%	19	44,2%	17	40,5%	17	42,5%	72	43,1%
Total	42	100,0%	43	100,0%	42	100,0%	40	100,0%	167	100,0%

p-valor =0,979

14.3.2.2.2. Controle

Abaixo temos as tabelas cruzadas entre as variáveis categóricas e a variável grupo.

Sexo (0=M, 1=F)	visf_q_contr								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
M	3	18,8%	6	42,9%	3	20,0%	5	33,3%	17	28,3%
F	13	81,3%	8	57,1%	12	80,0%	10	66,7%	43	71,7%
Total	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,4568

Cor (0=Branco;1=Pardo;2=Negro;3=Amarelo)	visf_q_contr								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
Branco	14	87,5%	11	78,6%	11	73,3%	8	53,3%	44	73,3%
Pardo	2	12,5%	1	7,1%	1	6,7%	4	26,7%	8	13,3%
Negro	0	0,0%	1	7,1%	0	0,0%	0	0,0%	1	1,7%
Amarelo	0	0,0%	1	7,1%	3	20,0%	3	20,0%	7	11,7%
Total	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,2219

Fumo	visf_q_contr								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%
Total	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%

AF DM1	visf_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%
Total	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%

AF DM2	visf_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%
Total	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%

AF HAS	visf_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	10	62,5%	7	50,0%	8	53,3%	8	53,3%	33	55,0%
S	6	37,5%	7	50,0%	7	46,7%	7	46,7%	27	45,0%
Total	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,9237

AF DLP	visf_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	7	43,8%	9	64,3%	8	53,3%	7	46,7%	31	51,7%
S	9	56,3%	5	35,7%	7	46,7%	8	53,3%	29	48,3%
Total	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,6937

AF Obesidade	visf_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	9	56,3%	11	78,6%	14	93,3%	10	66,7%	44	73,3%
S	7	43,8%	3	21,4%	1	6,7%	5	33,3%	16	26,7%
Total	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,1042

AF IAM/AVC precoce	visf_q_contr								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	15	93,8%	12	85,7%	15	100,0%	14	93,3%	56	93,3%
S	1	6,3%	2	14,3%	0	0,0%	1	6,7%	4	6,7%
Total	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,4551

HAS (0=N;1=S)	visf_q_contr								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	7	87,5%	9	100,0%	7	100,0%	6	100,0%	29	96,7%
S	1	12,5%	0	0,0%	0	0,0%	0	0,0%	1	3,3%
Total	8	100,0%	9	100,0%	7	100,0%	6	100,0%	30	100,0%

p-valor =0,7019

FTO rs9939609_cat	visf_q_contr								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
A/A	2	12,5%	2	14,3%	0	0,0%	2	13,3%	6	10,0%
A/T	11	68,8%	4	28,6%	12	80,0%	7	46,7%	34	56,7%
T/T	3	18,8%	8	57,1%	3	20,0%	6	40,0%	20	33,3%
Total	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,0768

FTO_A	visf_q_contr								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	3	18,8%	8	57,1%	3	20,0%	6	40,0%	20	33,3%
S	13	81,3%	6	42,9%	12	80,0%	9	60,0%	40	66,7%
Total	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,1017

FTO_T	visf_q_contr								Total	
	1 quartil		2 quartil		3 quartil		4 quartil			
	N	%	N	%	N	%	N	%	N	%
N	2	12,5%	2	14,3%	0	0,0%	2	13,3%	6	10,0%
S	14	87,5%	12	85,7%	15	100,0%	13	86,7%	54	90,0%
Total	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,5602

Visf rs9770242_cat	visf_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
A/A	11	68,8%	11	78,6%	11	73,3%	11	73,3%	44	73,3%
A/C	4	25,0%	3	21,4%	3	20,0%	4	26,7%	14	23,3%
C/C	1	6,3%	0	0,0%	1	6,7%	0	0,0%	2	3,3%
Total	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =1

Visf_A	visf_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	1	6,3%	0	0,0%	1	6,7%	0	0,0%	2	3,3%
S	15	93,8%	14	100,0%	14	93,3%	15	100,0%	58	96,7%
Total	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =1

Visf_C	visf_q_contr									
	1 quartil		2 quartil		3 quartil		4 quartil		Total	
	N	%	N	%	N	%	N	%	N	%
N	11	68,8%	11	78,6%	11	73,3%	11	73,3%	44	73,3%
S	5	31,3%	3	21,4%	4	26,7%	4	26,7%	16	26,7%
Total	16	100,0%	14	100,0%	15	100,0%	15	100,0%	60	100,0%

p-valor =0,9754

16. Anexo V - Artigo 2

10

Obesity in the Natural History of Type 1 Diabetes Mellitus: Causes and Consequences

Fernando Valente[1], Marília Brito Gomes[2]
and Sérgio Atala Dib[1]
[1]*São Paulo Federal University, São Paulo*
[2]*State University of Rio de Janeiro, Rio de Janeiro*
Brazil

1. Introduction

There has been a worldwide epidemic increasing in the prevalence of sedentary, overweight and obesity that comes with modernity and urbanization (Wang et al., 2002). The consequence is the development of insulin resistance (IR) and type 2 diabetes (T2D). This is classically defined as a metabolic disease that occurs due to a higher IR that leads to a slow setting of lower insulin production (more relative than absolute), in general in adult age. T2D is associated also with a genetic predisposition. The majority of T2D individuals are overweight or obese and the ones who do not, at least present increased abdominal adipose mass (ADA, 1997). The rising prevalence of overweight and obesity is happening also in children and adolescents (Pinhas-Hamiel et al., 1996; Willi & Egede, 2000; Rosenbloom et al., 1999). The metabolic syndrome (MS), which physiopathology is based on IR, shows the same trend in children and adolescents (Jago et al., 2008), as well as isolated pre-diabetes (Li et al., 2009).
In parallel, it has been seen an elevation in the number of type 1 diabetes (T1D) cases and its establishment at a younger age (EURODIAB ACE Study Group, 2000). T1D is characterized primarily by a pancreatic beta cell destruction, which may lead to ketosis. It can be classified as autoimmune (with positive anti-islet, anti-insulin, anti-GAD, anti-IA2 and/or anti-IA2 beta antibodies) or idiopathic, in which no autoantibodies can be detected, and occurs more frequently in individuals of African-American or Asian origin. Multiple genetic predisposition and environmental factors are involved with T1D (ADA, 1997). At least one of those autoantibodies is present in 85-90% of T1D on diagnosis. The treatment for T1D consists of multiple insulin injections, known as intensive treatment, to obtain adequate glycemic control and therefore prevent micro (The DCCT Research Group, 1993) and macrovascular (Nathan et al., 2005 and 2003) chronic complications. However, it can be followed by weight gain most of the times (Arai et al., 2008), which can amplify the risk of cardiovascular disease (CVD) in spite of good glycemic control. This weight gain can start on puberty and persist along adulthood (Särnblad et al., 2007). Therefore, some of these patients present clinical features of both T1D and T2D, confounding its classification. This phenotype was initially called double diabetes (DD) (Libman & Becker, 2003; Becker et al.,

2001), and is characterized by positive pancreatic autoantibodies in patients with clinical features of T2D, as IR and overweight and/or obesity (Pozzilli & Buzzetti, 2007; Gilliam et al., 2005; Reinehr et al., 2006), as shown in Table 1 (Pozzilli & Buzzetti, 2007) and in Figure 1.

	T1D	DD	T2D
Age at disease onset	Childhood +++ Adolescence +++ Adult +	Childhood ++ Adolescence ++ Adult (LADA) +	Childhood + Adolescence ++ Adult +++
Major genetics predisposition	MHC class I and II, *InsVNTR*, *CTLA-4*, *PTPN22*	?	*APM1*, *PPARγ 2*, *PtdCho-1*, *TCF7L2*
Environmental factors	Diet, viruses Cow´s milk in infancy	Life style (diet, sedentary life)	Life style (diet, sedentary life)
Circulating antibodies to β cells	+++	+	-
T cell-mediated immunity to β cells	+++	++	-
C-peptide secretion	-	+	+++
IR	-/+	++	+++
Inflammatory markers (cytokines, adipokines)	+	++	+++
Macrovascular complications	+	++	+++

Table 1. Clinical and pathogenic features of DD compared to T1D and T2D (Pozzilli & Buzzetti, 2007).

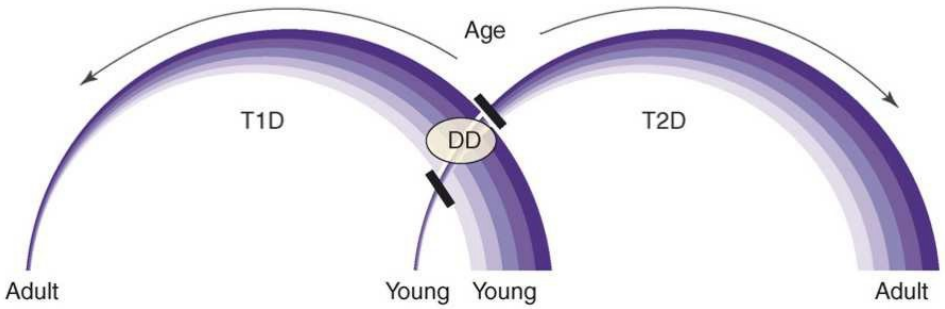

Fig. 1. Schematic representation showing where DD lies in respect to age and the two types of diabetes, as illustrated by two 'rainbows' (Pozzilli & Buzzetti, 2007).

2. Obesity as a accelerate factor to type 1 diabetes mellitus development

Studies with streptozotocin-induced diabetic baboons showed that to have an abnormal glucose tolerance it is necessary an isolated huge loss of beta-cell mass or a moderate loss of these cells associated to an IR (McCulloch et al., 1991), that could be in humans the physiologically IR of adolescence (Acerini et al., 2000) or gestation (Buschard et al., 1987), periods with higher incidence of T1D, or pathological situations like infection (usually one of the triggering factors of T1D) or weight gain.

Others studies suggest that the increase in the body mass index (BMI) and the consequent IR may accelerate the β cell destruction process in individuals predisposed to T1D, due to the release of obesity-related cytokines that show inflammatory and/or immunomodulatory properties (Aldhahi & Hamdy, 2003), triggering diabetes. This hypothesis may be reinforced by one study that correlated high anti-GAD levels with high BMI (Rolandsson et al., 1999). Two interesting data from studies with non-obese diabetic (NOD) mice are that hyperinsulinemia, an IR marker, precede clinical T1D (Armani et al., 1998) and that T1D incidence falls after treatment with rosiglitazone, an insulin sensitizer drug (Beales & Pozzili, 2002).

The IR, autoimmunity and apoptosis of the β cells constitutes the three factors of the called "accelerator hypothesis", proposed by Wilkin (Wilkin, 2001), that contemplate the factors presented in both more common types of diabetes, that is, T2D and T1D. There is a constitucional (intrinsic) high speed of apoptosis of β cells that is necessary to the development of diabetes, but rarely enough. The other two factors, extrinsic, that can speed the apoptosis of beta-cells are IR (result of weight gain and/or physical inactivity) and autoimmunity against beta-cells.

It is known that obese individuals have elevated serum levels of leptin, a cytokine secreted by adipocytes in proportion to adipose tissue mass and that is responsible, among other functions, for regulating food intake and thus BMI. Moreover, leptin controls the cellular immune response and is involved in the pathogenesis of autoimmune diseases (Lord, 2002). Studies have shown that administration of leptin in NOD mice promoted an early inflammatory infiltrate in the pancreatic islets, increased production of interferon gamma (IFN-gamma) by T lymphocytes, which accelerated the establishment of a T1D (Matarese, 2002 e 2005).

On the other hand, adiponectin, another important cytokine produced by adipose tissue, inversely proportional to its fat mass, can decrease the systemic and pancreatic islets inflammatory process, acting as a protective factor in the development of T1D, in addition to reducing IR (Kadowaki et al., 2006; Wellen & Hotamisligil, 2005).

However, development report (OECD, 2009) from 16 countries does not show any obvious relationship between national estimates of childhood obesity prevalence and incidence rates of T1D (Table 2). Therefore, obesity does not account for the wide between-country differences in T1D incidence, which range from 0.57 per 100 000 person-years in China to more than 48 per 100 000 person-years in Sardinia and Finland in the 0- to 14-year age group (Daneman, 2006).

On the other hand, in a meta-analysis of nine studies (eight case–control studies and one cohort study) comprising a total of 2658 cases (Verbeeten et al., 2011), seven reported a significant association between childhood obesity, BMI or %weight-for-height and increased risk for T1D. Four of these studies reported childhood obesity as a categorical exposure and

produced a pooled odds ratio of 2.03 (95% CI 1.46–2.80) for subsequent T1D, but with age at obesity assessment varying from age 1 to 12 years (Figure 2). A dose–response relationship was supported by a continuous association between childhood BMI and subsequent T1D in a meta-analysis of five studies (pooled odds ratio 1.25 (95%CI 1.04–1.51) per 1 SD higher BMI) (Figure 3).

Country	T1D incidence rate in children aged 0-14 years (per 100.000 person-years)	% of children aged 11-15 years overweight or obese
Finland	57,4	15,8
Sweden	41	10,5
Norway	27,9	10
UK	24,5	12
Denmark	22,2	9,7
Canada	21,7	21,3
USA	20,8	29,8
Netherlands	18,8	8
Germany	18	12
Ireland	16,3	14,2
Iceland	14,7	14,5
Spain	13	16,7
Poland	12,9	11,2
France	12,2	10,5
Greece	9,9	18,8
Italy	8,4	18,3

Table 2. Relationship between Type 1 diabetes incidence and prevalence of childhood overweight or obesity in 16 Organization for Economic Co-Operation and Development (OECD) countries, from Health at a Glance 2009: OECD Indicators (OECD, 2009).

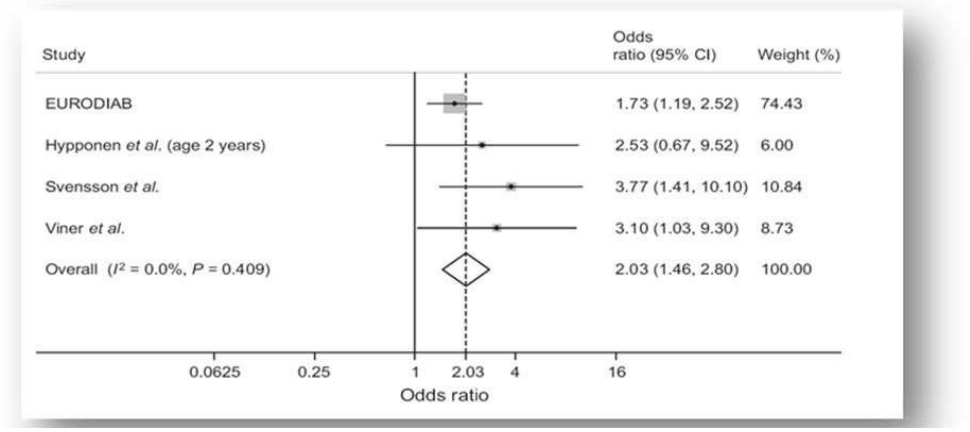

Fig. 2. Meta-analysis (fixed-effects inverse variance model) of studies of childhood obesity as a risk factor for subsequent T1D (Verbeeten et al., 2011).

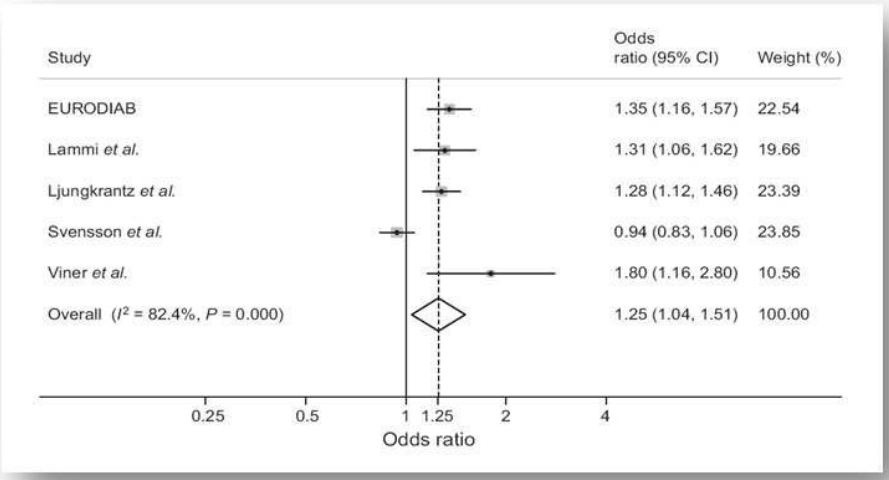

Fig. 3. Meta-analysis (random-effects inverse variance model) of studies of childhood BMI as a risk factor for subsequent T1D. Odds ratios correspond to a 1-unit increase in BMI standard deviation score (SDS)(Verbeeten et al., 2011).

3. Obesity after clinical Type 1 diabetes diagnostic

If on one hand intensive insulin prevents microvascular and macrovascular complications associated with poor glycemic control, the other brings an increased risk of severe hypoglycemia and weight gain, traditionally viewed as a normalization of weight, i.e. the correction of glycosuria, diuresis, and wasting with the initiation of insulin therapy. Insulin stimulates lipogenesis, inhibits protein catabolism, and slows basal metabolism. Other important aspect is the abnormal physiological route of insulin via its peripheral administration in those with T1D, which is also associated with reduced energy metabolism (Charlton & Nair, 1998). Classically normal or underweight, the phenotype of the T1D individuals is thus changing. A follow-up of 18 years of 589 individuals from the Pittsburgh Epidemiology of Diabetes Complications Study (EDC), a cohort of childhood-onset T1D, showed an increase in the prevalence of overweight by 47% (from 28.6% at baseline to 42%) and of obesity by sevenfold (from 3.4% at baseline to 22.7%), concomitantly with the highest prevalence of intensive insulin therapy - 7% and 82% were on intensive insulin therapy (≥ 3 insulin injections per day or on insulin pump) at baseline and 18 years after, respectively (Conway et al., 2010). Although injection frequency increased, total daily insulin dose decreased from 0.76 to 0.62 U/kg/day. Figure 4 shows the temporal patterns in the prevalence of being overweight and obese and the use of intensive insulin treatment, and these data was not influenced by the aging of the cohort and survivorship, as can be seen on Table 3. (age-group-specific prevalence for the 40–49-year-old age group by time period): overweight or obesity were present in 25% of the T1D individuals in 1986–1988 and in 68.2% in 2004– 2007 (Conway et al., 2010).

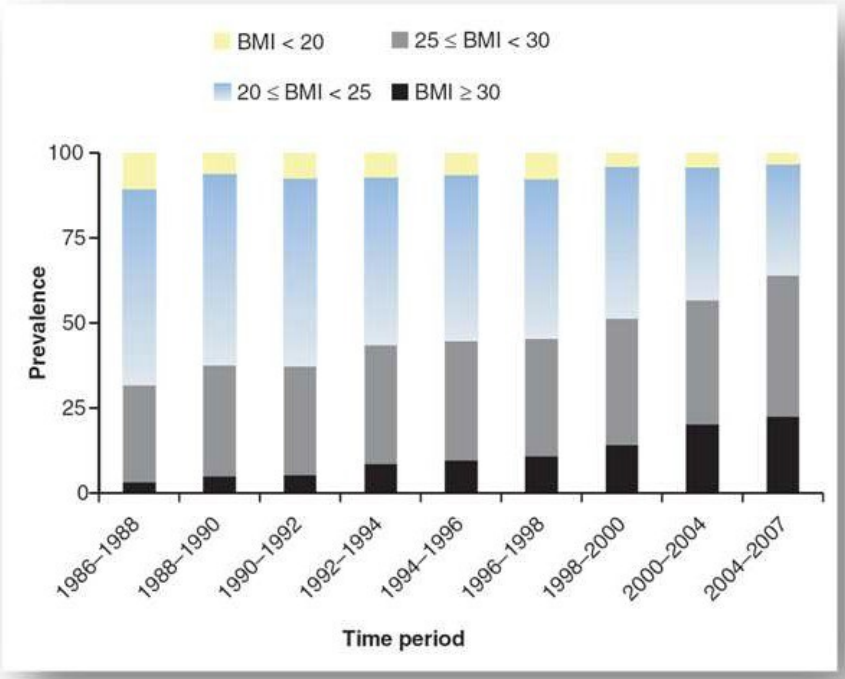

Fig. 4. Temporal patterns in overweight and obesity in Type 1 diabetes (Conway et al., 2010).

	BMI < 20 kg/m² (underweight)	20 ≤ BMI < 25 kg/m² (normal weight)	25 ≤ BMI < 30 kg/m² (overweight)	BMI ≥ 30 kg/m² (obese)
1986–1988	4 (9.1)	29 (65.9)	10 (22.7)	1 (2.3)
1988–1990	3 (5.8)	29 (55.8)	17 (32.7)	3 (5.8)
1990–1992	6 (8.5)	43 (60.6)	18 (25.4)	4 (5.6)
1992–1994	10 (12.2)	39 (47.6)	27 (32.9)	6 (7.3)
1994–1996	14 (11.9)	58 (49.2)	35 (29.7)	11 (9.3)
2004–2007	5 (2.9)	50 (28.9)	79 (45.7)	39 (22.5)

Table 3. Age-specific prevalence of underweight, normal weight, overweight, and obese for those aged 40-49 years in each time period, n (%)(Conway et al., 2010)

The prevalence of overweight/obesity in this T1D population was lower at baseline than general population (31.9 vs. 55.9%), although the incidence in both was similar after a mean of 7 years' follow-up (12%), and after 18 years' follow-up the prevalence of overweight in T1D people appear to have increased at a faster pace than in the general population.
Predictors of weight change were a higher baseline HbA1c, symptomatic autonomic neuropathy (inversely), overt nephropathy (inversely), and going onto intensive insulin therapy during follow-up. By the end of this study, 24% of the T1D people had died. Thus, as overt nephropathy and symptomatic autonomic neuropathy are associated with weight loss, the survivors are biased toward weight gain. The EDC Study also showed that, in T1D with a higher baseline HbA1c, moderate weight gain did not adversely affect the cardiovascular risk profile and favorably influenced the lipid profile in the setting of ameliorated glycemic control, but increased LDL cholesterol levels in the absence of a major improvement in glycemic control (Williams et al., 1999). Subjects who gained the least weight had the lowest LDL cholesterol levels at the follow-up period regardless of changes in HbA1 category. But when the weight gain after insulin was great, case of part of the patients who received intensive treatment in the Diabetes control and complications trial (DCCT) study and placed in the highest quartile of change in BMI, there was unmasking of central obesity or even MS in T1D (Purnell et al, 1998). These patients gained an average of 14 kg during the course of the study, about twice the weight gain equivalent to the third quartile of intensive care and the last quartile of patients on conventional treatment. Patients with the highest weight gain had the highest values of waist-hip ratio, blood pressure and insulin requirements when compared to the group with the same degree of glycemic control and also in intensive care, but who did not gain much weight. These youngsters also had a relatively atherogenic lipid profile, with elevations to levels of triglyceride, LDL cholesterol and apolipoprotein B (apoB) compared to their peers, also intensively treated, but without similar weight gain. The DCCT study (Purnell et al., 2003) also showed that the presence of family history of T2D was one of the strongest predictors for the weight gain in individuals with T1D who underwent intensive insulin therapy in the DCCT. In individuals with a family history of T2D, the weight gain, the final weight, the central fat distribution assessed by waist circumference, the insulin dose (units/kg/day) and degree of dyslipidemia were higher than in those without history familial T2D. Dyslipidemia included increases in triglycerides (TG) in VLDL particles and IDL (intermediate-density lipoprotein), which changes are common in individuals with central adiposity (Terry et al., 1989) and T2D (Brunzell & Chait, 1997). This could correspond to the expression of genes predisposing to T2D in this population. The findings of this study support the hypothesis that insulin treatment allows the expression of various components of MS in individuals with T1D who have family history of T2D, but also suggests that this group should be monitored more closely and earlier in relation to their potential of developing macrovascular complications, which is responsible for most of the increase in mortality found in patients with T1D (Laing et al., 1999), more than three times the general population.

4. Type 1 diabetes and Metabolic Syndrome

The insulin resistance is a soil to MS development and it is present during T1D evolution, even because of weight gain or because of the glucotoxicity – there was shown a proportion

between fasting glycemic and IR, and improvement of glycemic control is linked to better insulin sensitivity, for example contributing to the so-called period of "honeymoon", the remission phase of diabetes, well known by clinicians, and may occur in up to 50% of patients during the first year of disease (DCCT Research Group, 1987). Yki-Jarvinen et al. (1986), studied insulin sensitivity using the hyperinsulinemic euglycemic clamp in 15 adult patients with T1D and normal BMI during the first 2 weeks, 3 months and 1 year after clinical diagnosis. In the first two weeks of diagnosis, they had a decrease in insulin sensitivity when compared to controls. However, three months after diagnosis, there was an improvement in insulin sensitivity in these patients, and it became similar to that of controls. Importantly, this improvement in insulin sensitivity coincided with the period of "honeymoon" in these patients, and showed a good correlation with HbA1c values and insulin doses in the treatment. Insulin sensitivity of patients who entered clinical remission was 40% greater than those who did not have this condition. Recently, our group performed a cohort and multicenter study (Gabbay et al, 2005; Dib, 2006) to determine the prevalence of MS in a group of patients with T1D and assessing their relation with the time of diagnosis. The study included 524 (276 females) T1D (according to the criteria of the Brazilian Diabetes Society and American Diabetes Association) with an average age of 20 ± 9 years and divided according to the time of T1D in 4 groups: GI, ≤ 5 years (n = 264), G-II, 6-10 years (n = 108), G III, 11-15 years (n = 96) and G IV,> 15 years (n = 56). In these groups were analyzed BMI (kg/m^2), total daily doses of insulin for treatment (U/kg/day), HbA1c values and the prevalence of MS. The criterion used for characterization of MS was the one of the World Health Organization, that is, diabetes mellitus and 2 or more of the following: increase in waist circumference (criterion set for youth) (Freedman et al., 1999), TG ≥ 150 mg/dL or HDL-C < 40 mg/dL (males) and < 50 mg/dL (females), urinary albumin excretion (≥ 20 μg/min) and hypertension (according to criteria adjusted for age and sex) (Brazilian Hypertension, Heart and Nephrology , Societies 2002). The daily insulin dose and HbA1c values were significantly lower in G-I than in other groups (G-I: 0.7 ± 0.3, G-II: 1.1 ± 0.3, G- III: 1.0 ± 0.3 and G-IV: 0.8 ± 0.2 U/kg/day, p = 0.000) and (G-I: 8.7 ± 2.6, G-II: 9.5 ± 2.2, G-III,
9.5 ± 2.3 and G-IV: 9.4 ± 2.8%, p = 0.000), respectively. There was a significant increase in the values of waist circumference (G-I: 71.9 ± 2.2, G-II: 75.7 ± 11.1, G-III: 76.5 ± 8.4 and G-IV: 80.2 ± 7.5 cm, p = 0.000) and BMI (G-I: 20.6 ± 3.8, G-II: 22.4 ± 3.6, G-III: 22.5 ± 3.1 and G- IV: 23.1 ± 4.1 kg/m2, p = 0.000) after 5 years of diagnosis of T1D. However, it is important to note that the BMI values were not superior to classical criteria of obesity or even overweight. The prevalence of MS (G-I: 5.1, G-II: 11.2, G-III: 18.9 and G-IV, 31.5%, p = 0.000) increased with time of diagnosis (Figure 5). The odds ratio (OR) for the development of MS in the other groups in relation to G-I was significant G-III onwards, being equal to 3.59 and 7.18 for this for G-IV in relation to G-I, both with p = 0.001. That is, the odds for the development of MS in patients with T1D and over 15 years of diagnosis is 618% higher than under 5 years of disease. Similarly, the odds for the development of MS for patients with T1D between 11 and 15 years duration is 259% higher than those with less than 5 disease in this group of patients. Other factors related to insulin resistance, such as visceral fat, BMI and TG, even when considered separately, also increased with the duration of the disease.

In another study (Giuffrida et al., 2005), 500 T1D patients [age 19.7 ± 8.9 years (mean ± SD), 52% female], we observe that, also analyzed separately, the prevalence of microalbuminuria (GI: 24.1%, G-II, 25.0%, G-III: 31.0% and G-IV: 55.6%, p <0.05) and hypertension (GI, 8.3%;

G-II: 13.6%, G-III: 28.6% and G-IV: 44.4%, p = 0.000) increased with duration of disease. Data from these studies suggest that chronic glucotoxicity (elevated HbA1c) and factors involved in diabetic nephropathy (microalbuminuria and hypertension) may be one of the mechanisms for the development of MS in T1D, among many others.

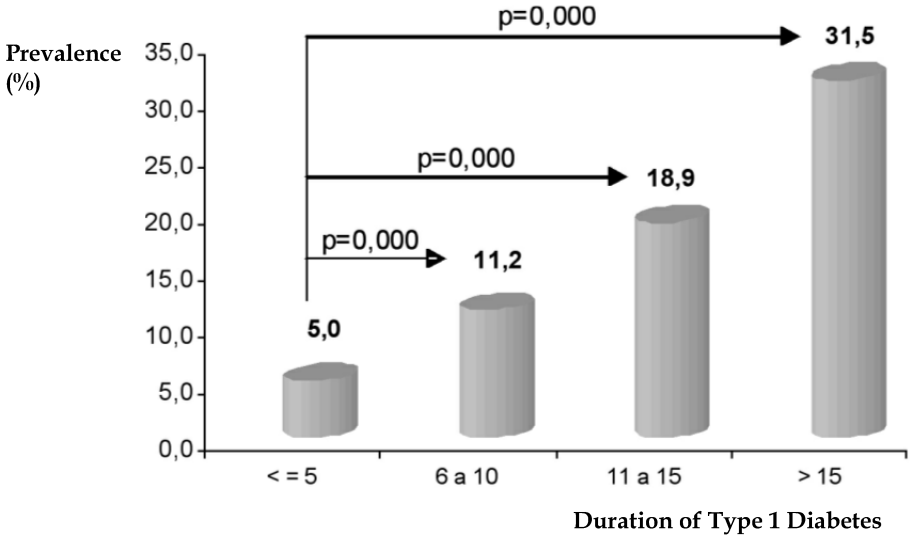

Fig. 5. Prevalence of MS in patients with T1D, according to disease duration. (Dib, 2006)

Aiming to compare the prevalence of MS using the ATP III criteria modified for age in our group of T1D, we studied 521 (51.2% female, age 20 ± 9 years; time of diagnosis of diabetes: 7.7 ± 6.9 years and HbA1c: 9.0 ± 2.4%) and found that this was equal to 12% (unpublished data).

The lowest concentration in the insulin in the liver causes a decrease in the synthesis of GHBP levels (Growth Hormone Binding Protein) (Bereket et al., 1999) that leads to a decrease in GH action, in the values of IGF-1 and in the inhibitory counter-regulation of this hormone, resulting in an exaggerated secretion of GH and increased insulin resistance.

The realization of a strict glycemic control in T1D, according to current guidelines, many often leads to use of supraphysiological doses of insulin, which could result in a stimulation of androgen synthesis, mediated by insulin, as occurs in cases of insulin resistance. Accordingly, the prevalence of Polycystic Ovary Syndrome (PCOS) and other symptoms and signs of hyperandrogenism were evaluated in a group of 85 patients with T1D (Escobar- Morreale et al., 2000). PCOS was defined by the presence of menstrual changes and clinical or laboratory evidence of hyperandrogenism. Other causes of elevated androgen hormones were excluded. Eighteen normal eumenorrheic women served as controls. Thirty-three patients (38%) presented with T1D changes associated with an androgen excess (16 with PCOS and 17 with hirsutism without menstrual abnormalities). The patients with T1D and PCOS had elevated total and free testosterone and androstenedione but normal levels of sex-hormone binding globulin (SHBG) and dehydroepiandrosterone sulfate (DHEAS). However, despite the finding of a high prevalence of hyperandrogenism (including PCOS and hirsutism), there was no difference between clinical variables such as duration of

diabetes, age at diagnosis, conventional or intensive insulin treatment, average daily dose of insulin or glucose control between the T1D patients with and without hyperandrogenism in study.

The gold-standard method for evaluating IR is the hyperinsulinemic euglycemic clamp that directly measures the relationship between blood glucose and insulin levels, but it is difficult to be executed on a large scale since it is an invasive and expensive procedure. For this reason, HOMA-IR is used as a surrogate method to indirectly measure IR, calculated through fasting glycemia and insulinemia relationship. On the other hand, this calculation cannot be used for T1D as these patients do not produce endogenous insulin. So to evaluate the insulin sensitivity in these patients eGDR calculation (Equation 1) was developed that shown a good correlation with hyperinsulinemic euglycemic clamp (Chillarón et al., 2008):

$$eGDR\ (mg.kg\text{-}1.min\text{-}1) = 24{,}4 - 12{,}97\ (W/H) - 3{,}39\ (Hypertension) - 0{,}60\ (HbA1c) \quad (E1)$$

In which W/H is the waist-hip ratio(cm), hypertension is the presence or absence of hypertension (0 = no and 1 = yes) and the value of HbA1c is represented in %. It is also a good predictor of mortality, coronary arterial disease (CAD), microalbuminuria - a precocious hallmark of endothelial dysfunction (Pambianco et al., 2007) – and MS for T1D individuals, according to IDF (International Diabetes Federation), WHO (World Health Organization) and NCEP/ATPIII modified by AHA (American Heart Association).

As we know the insulin resistance is linked to an ectopic store of fat in insulin sensitive tissues like liver and muscle, but it is not clear if this fat accumulation leads to a hyperinsulinemic state or if it is its consequence. In a study with T2D patients, the glycemic control obtained after 67 hours of insulin treatment caused an accrual in intramyocellular and intrahepatic lipid content measured by nuclear magnetic resonance (NMR) spectroscopy, without compromising insulin sensitivity (Anderwald et al., 2002). Like T2D individuals, the intramyocellular lipid content in T1D ones was increased compared to controls and there was a direct relation with the glycemic control (Sibley et al., 2003).

There has been also noted a clear association between IR and visceral fat store, that can take its content extended in consequence of intensive insulin treatment independently of the type of diabetes, aggravating the CVD risk. In the DCCT study, the subgroup of T1D individuals that received intensive insulin treatment had a higher growth in BMI compared to the ones who were treated conventionally and it was noted a stronger correlation of this BMI variation with visceral fat deposit than with subcutaneous fat (Sibley et al., 2003). In this study, there are also demonstrations of direct association between visceral fat content and hepatic lipase, which favors the emergence of atherogenic dyslipidemia in these intensive treated individuals that put on more weight, reaching lipid levels similar to those of the conventionally treated group, suggesting loss of the benefits of intensive insulin therapy on lipids in this group of patients who had an excessive weight gain.

In other study (Nadeau et al., 2010), lean T1D adolescents with short time of disease (average of 7.5 years) without any inflammatory, clinical or lipid abnormalities had a IR - measured by hyperinsulinemic euglycemic clamp - similar to non diabetic obese adolescents and a superior IR than control subjects matched for age, pubertal stage, physical activity level and BMI, despite normal waist and intramyocellular lipid content.

There was also a demonstrated association between fat mass and blood pressure levels in T1D children and adolescents – high fat content, identified by the bioimpedance (BIA), and BMI were related to higher systolic and diastolic blood pressure (Pietrzak et al., 2009). The BIA is an easy, noninvasive, portable, no risk, relatively inexpensive method to measure the percentage of fat and provides results comparable to dual energy X-ray absorptiometry (DXA) (Elberg et al., 2004; Völgyi et al., 2008), that is reliable but expensive, requiring trained operators, individuals exposed to ionizing radiation and is not portable (Thomson et al., 2007).

There are data indicating good correlation between BIA and DXA, including Brazilian (Braulio et al., 2010) and T1D subjects (Leiter et al., 1994). Although overestimating the percentage of fat in lean individuals and underestimate it in obese (Sun et al., 2005), proves useful for predicting metabolic risk (including IR) as well as BMI and waist circumference (Lee et al., 2008). Through the BIA, it is possible to calculate the CDI (central fat distribution index), which assesses the impact of subcutaneous fat in the central fat distribution, and can be measured by dividing the area of abdominal subcutaneous fat mass by total fat (Silva et al., 2009). This measure seems to be relevant in that, according to some studies (Silva et al., 2009; Van Harmelen et al., 1998), the main source of leptin is the abdominal subcutaneous adipose tissue, either by mass effect - the subcutaneous adipose tissue is the major fat depot - as to produce more leptin (larger cell size and leptin gene expression) that omental adipose tissue. However, depending on the impedance (eg the trunk), the results may vary according to position changes, skin temperature, variation in electrode impedance and errors in their placement (Scharfetter et al., 2001).

A new adipokine identified visfatin, increases in proportion to visceral fat mass (Fukuhara et al., 2005) and decreases after gastric band placement (Haider et al., 2006). It is high in individuals with T2D (Chen et al., 2006) and even more in T1D (López-Bermejo et al., 2006), suggesting that its rising is linked to deterioration of pancreatic β cells. In vitro, visfatin activates the insulin receptor regardless of fasting state, increasing glucose uptake in muscle and adipose tissue and reducing hepatic glucose production independently of insulin levels (Fukuhara et al., 2005).

Hyperhomocysteinemia, known risk factor for coronary atherosclerosis (Okada et al., 1999), has also been shown to be detrimental to pancreatic insulin secretion (Patterson et al., 2006).

The C-reactive protein (CRP), an inflammatory marker that confers increased risk for atherosclerosis (Hayaishi-Okano et al., 2002), is increased in T2D patients (Nabipour et al., 2008) and obese subjects (Richardson et al., 2009), and also relates to the control of diabetes (King et al., 2003), i.e. may increase due to the weight gain caused by intensive control of diabetes (Schaumberg et al., 2005).

Ferritin is another acute phase inflammatory marker, correlate positively with CRP and BMI (Richardson et al., 2009), and also more specifically with visceral adiposity and insulin resistance (Iwasaki et al., 2005), leading to increased ferritin levels in T2D patients, concurrent with an augmentation of visfatin (Fernandez-Real et al., 2007).

Recently, several studies have indicated that the gene associated with fat mass and BMI (FTO) has an important genetic effect on BMI and risk of obesity through the rs9939609 polymorphism. This polymorphism is linked to an impaired responsiveness to satiety, ie have an effect on appetite (Wardle et al., 2008). The homozygous AA genotype results in an average gain of 3 kg or 1 unit of BMI over the TT genotype. There is evidence that this

polymorphism is linked to BMI gain in subjects with T1D (Gu et al., 2010) and higher levels of leptin and CRP (Welsh et al., 2010).

5. Conclusion

Obesity may both contribute to the onset of T1D as being a consequence of intensive treatment with insulin, that is, good glycemic control in T1D can lead to excessive weight gain in predisposed individuals (eg relatives of T2D), IR and consequently MS. Thus, the current approach of patients T1D should happen as it is done in T2D, multifactorial with an early and intensive monitoring of lifestyle, blood glucose, blood pressure and lipids, with the aim of identifying, correcting these factors and potentially reduce the high risk for cardiovascular disease in these patients. So gain weight can accelerate the presentation and modify the initial TID phenotype as increase the cardiovascular risk factors during evolution do the disease .

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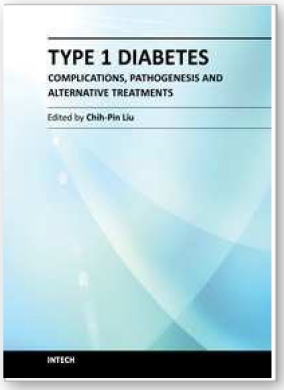

Type 1 Diabetes - Complications, Pathogenesis, and Alternative Treatments

Edited by Prof. Chih-Pin Liu

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This book is intended as an overview of recent progress in type 1 diabetes research worldwide, with a focus on different research areas relevant to this disease. These include: diabetes mellitus and complications, psychological aspects of diabetes, perspectives of diabetes pathogenesis, identification and monitoring of diabetes mellitus, and alternative treatments for diabetes. In preparing this book, leading investigators from several countries in these five different categories were invited to contribute a chapter to this book. We have striven for a coherent presentation of concepts based on experiments and observation from the authors own research and from existing published reports. Therefore, the materials presented in this book are expected to be up to date in each research area. While there is no doubt that this book may have omitted some important findings in diabetes field, we hope the information included in this book will be useful for both basic science and clinical investigators. We also hope that diabetes patients and their family will benefit from reading the chapters in this book.

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Phone: +86-21-62489820
Fax: +86-21-62489821

16. Anexo VI - Artigo 3

Relationship between short and long-term glycemic variability and oxidative stress in type 1 diabetes mellitus under daily life insulin treatment

[1] Departamento de Medicina, Divisão de Endocrinologia, Centro de Diabetes da Universidade Federal de São Paulo, São Paulo, SP, Brasil
[2] Departamento de Medicina, Divisão de Nefrologia, Universidade Federal de São Paulo, São Paulo, SP, Brasil

Tatiana Valente[1]
https://orcid.org/0000-0003-2066-4464

Fernando Valente[1]
https://orcid.org/0000-0001-8207-5521

Maria Beatriz Bastos Lucchesi[1]
https://orcid.org/0000-0002-7227-185X

Giovana Rita Punaro[2]
https://orcid.org/0000-0002-0833-1344

Margaret Gori Mouro[2]
https://orcid.org/0000-0002-6291-1016

Monica Andrade Lima Gabbay[1]
https://orcid.org/0000-0002-1300-9675

Elisa Mieko Suemitsu Higa[2]
https://orcid.org/0000-0001-5144-8903

Sergio Atala Dib[1]
https://orcid.org/0000-0001-8653-8773

ABSTRACT

Objectives: The purpose of this study was to investigate the heterogeneity of the association between glycemic variability and oxidative stress markers in T1DM patients under daily life insulin treatment. **Subjects and methods:** We studied, in a cross-sectional analysis, 76 T1DM patients without clinical chronic diabetes complications and 22 healthy individuals. Were evaluated the short-term glycemic variability (STGV), long-term glycemic variability (LTGV), oxidative stress markers [8-isoprostaglandin-F2α (Ur-8-iso-PGF2α), nitric oxide (NO), thiobarbituric acid reactive substances (TBARS) and erythrocytes reduced/oxidized glutathione (GSH/GSSG)] and biochemical dosages (glycaemia, HbA1c, lipidogram, albuminuria). **Results:** Plasmatic NO was positively associated with LTGV (last year average of HbA1c) (8.7 ± 1.6% or 71 ± 18 mmol) (rS: 0.278; p: 0.042). PlasmaticTBARS, erythrocytes GSH/GSSH and Ur-8-iso-PGF-2α didn't show correlation with glycemic variability. GSH/GSSG was inversely correlated with LDL-cholesterol (rS: - 0.417; p: 0.047) and triglycerides (rS: -0.521; p: 0.013). Albuminuria was positive correlated with age (rS: 0.340; p: 0.002), plasmatic NO (rS: 0.267; p 0.049) and TBARS (rS: 0.327; p: 0.015). **Conclusion:** In daily life insulin treatment, young T1DM patients have higher plasmatic NO than healthy subjects. However, the correlation between glycemic variability and oxidative stress markers is heterogeneous. Lipid profile and albuminuria are associated with different oxidative stress markers.These data collaborate to explain the controversial results in this issue. Arch Endocrinol Metab. 2021;65(5):570-8

Keywords
Glycemic variability; glycemic fluctuations; oxidative stress; type 1 diabetes

Correspondence to:
Tatiana Valente
Divisão de Endocrinologia,
Centro de Diabetes,
Universidade Federal de São Paulo
Rua Pedro de Toledo, 781, 12º andar
04039032 – São Paulo, SP, Brasil
valentetati@yahoo.com.br

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INTRODUCTION

Large randomized studies have established that early and persistent glycemic control during diabetes mellitus natural history, reduces the risk to develop both micro and macrovascular chronic complications of this disease (1). The initial and prolonged effect of overall glycemic control in this process is part of the "metabolic memory". This concept supports the adoption of a precocious, aggressive and continuous treatment approach, at least, since the clinical diabetes diagnosis (2).

It is known that persistent hyperglycemia results in overproduction of oxygen free radicals, which contributes to the beginning and progression of chronic diabetes complications (3). However, recent evidence suggests that acute glucose fluctuations may accelerate the development of diabetes chronic complications (4) more than chronic hyperglycemia (5), by triggering oxidative stress (6). Hyperglycemic spikes sometimes seems to be high enough to activate oxidative stress that persists during subsequent periods of normoglycemia, but too brief to affect the HbA1c (7). So far, there is no "gold standard" parameters for determining glucose variability (3). The Mean Amplitude Glucose Excursions (MAGE) is the most used for Continuous Glucose Monitoring System (CGMS), and standard deviation (SD) and/or coefficient of variation (CV) for self-monitoring blood glucose (SMBG) curves (3). Majority of studies are based on the 7-point glucose profiles, that may not capture the full degree of variability that is observed in the CGMS (8).

There is a paucity of studies on the effects of glucose fluctuations on routine clinical management and oxidative stress in patients with type 1 diabetes mellitus (T1DM) (9).

Many markers have been used to evaluate oxidative stress degree in patients with diabetes such as urinary 8-iso-prostaglandin-F2α (8-iso-PGF2α), glutathione, barbituric acid reactive substances (TBARS) and nitric oxide (NO).

8-iso-PGF-2α is a specific isoprostane formed from free radical oxidation of arachidonic acid and is an excellent reflection of activating oxidative stress throughout the body (10).

Glutathione is one of the key antioxidants involved in protecting cells from damage by reactive oxygen species. It exists in the body in its reduced (GSH) and oxidized form (GSSG), acting directly or indirectly in many important biological processes including protein synthesis, metabolism and cell protection (11). From the ratio of reduced glutathione/oxidized glutathione (GSH/GSSG) it is possible to do an analysis of the antioxidant defense system.

TBARS are reactive thiobarbituric acid substances that, in vitro, have proved as potent oxidative stress parameter. However, it is not a very sensitive method to evaluate oxidative stress (12).

Nitric oxide (NO) plays an important role in modulating endothelial function, with several antiatherogenic actions, however depending on the environment, it can be potentially toxic. NO is generated from oxide nitric synthase (NOS) of which there are three forms: two constitutive types [brain (bNOS) and endothelial (eNOS)] and one inducible type (iNOS). Glycemic fluctuations reduce eNOS activity and increase iNOS expression, leading to an overproduction of NO. Various impairments in NO pathways have been reported in T1DM both in animal models and humans (13). However, in vivo, it is not clear whether the defect is in basal or stimulated NO synthesis, NO bioavailability, responsiveness to NO, or perhaps all of these.

The aim of this study was to investigate the heterogeneity of the association between short and long term glycemic variability with markers of oxidative stress in patients with type 1 diabetes mellitus in real word.

SUBJECTS AND METHODS

Study design

Study protocol was approved by the local ethics committee of Federal University of São Paulo (CAAE registration number generated in Plataforma Brasil was 02703212.6.0000.5505) and participants or their legal guardians gave written informed consent.

It was a prospective study, conducted from 2013 to 2014 at Diabetes Center of São Paulo Federal University and enrolled 76 T1DM and 22 healthy controls individuals.

Inclusion criteria were T1DM patients aged between 12 and 45 years old, diagnosed for at least five years, without clinical chronic diabetes complications, and had at least two HbA1c in the last year from the same laboratory. Exclusion criteria were reported patients with subcutaneous continuous insulin infusion (CSII), infectious disease, during menstrual flush, pregnancy, smoking, and any inflammatory process in activity.

One hundred and thirty medical records were reviewed to select patients for the study. Fifty-four patients were ineligible because they presented some of the exclusion criteria. Seventy-six T1DM filled the criteria inclusion, were contacted by phone or during a routine clinical appointment and participated in the study. Twenty-one patients were excluded from some analysis because they didn´t follow the protocol, didn't collect blood sample or showed during randomization, any inflammatory or infectious disease. However, these 21 patients presented demographic characteristics like the other participants included.

Twenty-two controls without any chronic disease or other exclusion criteria, were enrolled for the study, and were adjusted for age and body mass index (BMI).

Study protocol

At subject study entry, a subcutaneous continuous glucose monitoring system (CGMS) sensor (Medtronic MiniMed®, Northridge CA, USA) was inserted subcutaneously into the abdominal region and calibrated.

Fingertip capillary blood glucose was measured at least three times per day and values were used to titrate CGM meters. The monitor was removed after three days, and data was downloaded and analyzed using CGMS Software version 3.0 (CA, USA). Eight to twelve hours fasting venous blood samples were collected on the Day 1 and 8 hours overnight urinary samples on Day 3 of this continuous interstitial glucose monitoring period. Collected blood samples were stored at -80°C until laboratory testing for analysis of oxidative stress biomarkers and other laboratory tests.

Glycemic variability

Short-term glycemic variability (STGV) was defined by standard deviation (SD) of glucose values during continuous subcutaneous glucose monitoring system (CGMS) over three consecutive days (between days). Long-term glycemic variability (LTGV) was accessed by mean glycated hemoglobin (HbA1c) of last year (visit to visit) (14). These measures were obtained in both T1DM patients and healthy controls.

Oxidative stress biomarkers

8-iso-prostaglandin-F2α

8-iso-PGF2α was measured by an enzyme-linked immunosorbent assay (ELISA) (EIA-catalog number ADI-I-900-010) (ALPCO-US) from individuals' eight hours overnight urinary samples. Urine was diluted fourfold with sample dilution buffer containing a final concentration of ~0.1 mM TPP (triphenylphosphine, 0.03-0.05 mg/mL). TPP is an antioxidant which looks like a precipitate in samples as it does not easily dissolve. Before using stored samples containing TPP, spin samples at 10,000 rpm for 5 minutes to separate the precipitated TPP and other particulates from sample solution. The inter-assay coefficient of variation was 11.3% and range between 600-1400 pg/mL.

Nitric oxide (NO)

Plasmatic NO was quantified using chemiluminescence method; Model 280 Nitric Oxide Analyzer (NOA™), Sievers Instruments, Inc. (Boulder, CO, USA), a high-sensitivity detector for measuring nitric oxide, based on gas-phase chemiluminescent reaction oxide between nitric oxide and ozone, as described elsewhere.

$$NO^{\cdot} + O_3 \rightarrow NO^{\cdot}_2 + O$$

$$NO^{\cdot}_2 \rightarrow NO_2 + h\nu$$

Emission of a photon from electrically excited nitrogen dioxide is in the red, near-infrared region of the spectrum and is detected by a thermoelectrically cooled red-sensitive photomultiplier tube. Sensitivity for measurement of NO and its reaction products in liquid samples is ≈1 pmol.

Thiobarbituric acid reactive substances (TBARS)

TBARS were determined by colorimetric method in plasma samples diluted with deionized water (1:5). Next, 1 mL of the diluted sample was transferred to glass tubes, 1 mL of trichloroacetic acid (TCA) 17.5% and 1 mL of thiobarbituric acid 0.6% (Sigma, St. Louis, MO, USA), pH 2 were added. Sample tubes were set in a water bath at 95°C for 20 minutes, and then cooled to room temperature. Next, 1 mL of TCA 70% was added and incubated for 20 minutes. Afterwards, incubated samples were centrifuged at 3,000 rpm for 20 minutes at 4°C and the absorbance read at 534nm on a microplate reader (Synergy HT, Biotek, Winooski, USA). TBARS concentration calculations were performed using the extinction coefficient, 1.56×10^5 mol^{-1} cm^{-1}, with plasma results expressed in nmol/ml.

Reduced/oxidized glutathione (GSH/GSSG)

Erythrocytes GSH/GSSG were measured by colorimetric assay (EnzyChrom GSH/GSSG Assay-EGTT-100) in a morning plasma sample collected after 8-12 hours fasting. This assay kit is designed to accurately measure total, reduced and oxidized glutathione in biological samples using an enzymatic method. Linear detection range 0.01-3 µM GSH equivalents with a detection limit of 10 nM GSH equivalents.

Other laboratory tests

Lipid profile, which includes total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides, were obtained by colorimetric assays of the 8-12 hour fasting

plasma samples. Glycated hemoglobin (HbA1c) was obtained from HPLC (nv: 4.0–5.6%) (TOSOH G7 Luxembourg, Belgium). Ferritin was determined by electrochemiluminescence (Access, Beckman Coulter) and C-reactive protein (CRP) by immunoturbidimetric assays (Olympus AU 640). Albuminuria was measured in an isolated overnight urine aliquot by immunoturbidimetric assay (two positives in three samples) (normal value <20 μg/min).

Statistical analysis

The sample size was calculated to get a power of 80% to detect a correlation ≥0.3 between variables studied, with α value of 5%.

Statistical evaluation was performed using Sigma Stat Version 3.5 (CA, USA). Numerical data were expressed as mean ± standard deviation. Parametric and nonparametric tests were used according to the distribution (normal or not, respectively) of the data studied.

For comparing two variables, when they presented an equal variance test, it was used the t-test. When equal variance test failed, it was used a Mann-Whitney test. To verify the relationship between quantitative variables was used the Spearman correlation coefficient. A p value < 0.05 was considered statistically significant.

RESULTS

Clinical and biochemical characteristics of controls and type 1 diabetes individuals studied are shown in Table 1. Age, BMI, STGV, LTGV, albuminuria, serum CRP and plasmatic NO were significantly different between controls and T1DM patients. Plasmatic NO was significantly higher in T1DM than controls (Figure 1), even after adjusted for age and BMI. There were no significant differences between the groups for gender distribution, serum lipid profile, ferritin, urinary 8-iso-PGF-2α, plasmatic TBARS and GSH/GSSG.

In the T1DM group STGV showed positive correlations with serum total cholesterol (rS: 0.227; p:0.05) and triglycerides (rS: 0.241; p:0.03) while recording an inverse correlation with age (rS: -0.239, p: 0.037).

LTGV (8.7± 1.6% or 71 ± 18 mmol/mol) showed a positive correlation with short-term glycemic variability (STGV) (rS: 0.361; p: 0.001), serum triglycerides (rS: 0.361; p: 0.001) and plasmatic NO (rS: 0.278; p: 0.042) (Figure 2).

Both serum LDL-cholesterol and serum triglycerides were inversely correlated with GSH/GSSG (rS: -0.417; p: 0.047 and rS: -0.521; p: 0.013, respectively) (Figure 3) in T1DM.

Table 1. The clinical and biochemical characteristics of controls and type 1 diabetes individuals studied

Characteristics	Controls	Type 1 diabetes	p value
N	22	76	
Age (years)	25.8 ± 3.9	23.6 ± 6.8	0.041
Gender (female/male)	15/7	35/41	0.090
Duration of T1DM (years)	----------	13.0 ± 6.0	
BMI (kg/m²)	22.1 ± 2.8	23.8 ± 3.6	0.045
Insulin Dose (U/kg/day)	----------	0.83 ± 0.28	
Cholesterol (mg/dL)	167.8 ± 29.9	164.4 ± 40.6	0.632
Triglycerides (mg/dL)	86.7 ± 43.8	103.3 ± 97.3	0.917
HDL cholesterol (mg/dL)	47.4 ± 13.8	44.5 ± 11.4	0.157
LDL cholesterol (mg/dL)	103.0 ± 27.2	100.3 ± 32.3	0.636
CRP (mg/L)	3.91 ± 2.72	4.99 ± 3.97	0.017
Ferritin (ng/mL)	104.9 ± 108.1	112.1 ± 100.9	0.571
Albuminuria (%)	0	17	0.042
STGV*	10.8 ± 1.7	74.5 ± 19.8	<0.001
LTGV**	5.4 ± 0.3 (35)	8.7 ± 1.6 (71)	<0.001
8-iso-PGF-2α (pg/mL)	1414.09 ± 557.14	941.22 ± 595.86	0.056
NO (μM)	63.8 ± 13.6	115 ± 104.1	0.004
TBARS (nmol/mL)	3.28 ± 1.62	3.35 ± 1.69	0.427
GSH/GSSG	4.73 ± 3.93	4.40 ± 3.14	0.857

*Standard Deviation (SD) over 3 consecutive days (CGMS). **Mean glycated hemoglobin (HbA1c) of the last year.

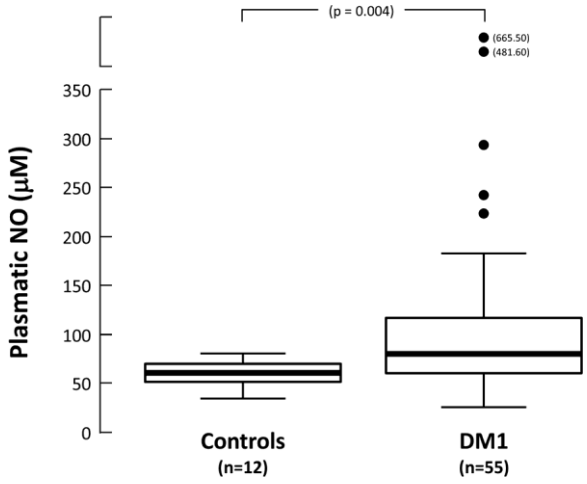

Figure 1. Distribution of plasmatic NO (µM) values found in the control and type 1 diabetes group (Bars = medium and SD of values).

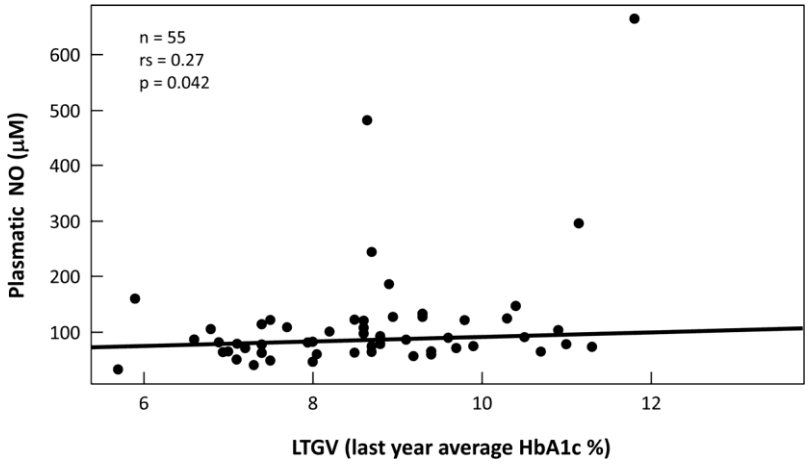

Figure 2. Correlation between plasmatic NO (µM) and LTGV (last year average HbA1c) (%) in T1DM.

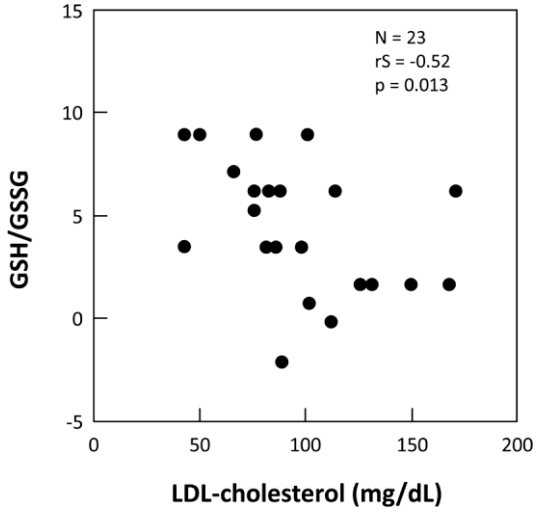

Figure 3. Correlation between GSH/GSSG and LDL-cholesterol in T1DM (mg/dL).

Albuminuria was significantly positive correlated with age (rS: 0.340; p: 0.002), plasmatic NO (rS: 0.267; p 0.049) (Figure 4) and plasmatic TBARS (rS: 0.327; p: 0.015) (Figure 5) in T1DM.

DISCUSSION

This study showed that plasmatic NO levels, an indicator of oxidative stress, were significantly higher in a subgroup of young adults with T1DM when compared to healthy age adjusted controls. However, the plasmatic TBARS and GSH/GSSG levels and urinary 8-iso-PGF2α excretion were similar between these two groups.

As expected, the glycemic variability was seven times higher in T1DM than in healthy controls. The glycemic excursions in these patients were positively correlated with plasmatic NO, while the lipid profile inverse correlated with GSH/GSSG and albuminuria positively correlated with plasmatic NO and TBARS.

The results regarding the relationship between glycemic variability and oxidative stress in T1DM are plenty and heterogeneous in the literature (15). In this present study, the only oxidative stress biomarker associated with long-term glycemic variability (LTGV) was the plasmatic NO levels. The others oxidative stress biomarkers studied didn´t show any correlation with glycemic variability.

It has been described that T1DM have reduced NO bioavailability or diminished vascular response to NO, either because it is destroyed more rapidly by superoxide or due to decreased target enzyme responses. Therefore, basal NO synthesis must increase to maintain an equivalent level of basal NO-mediated

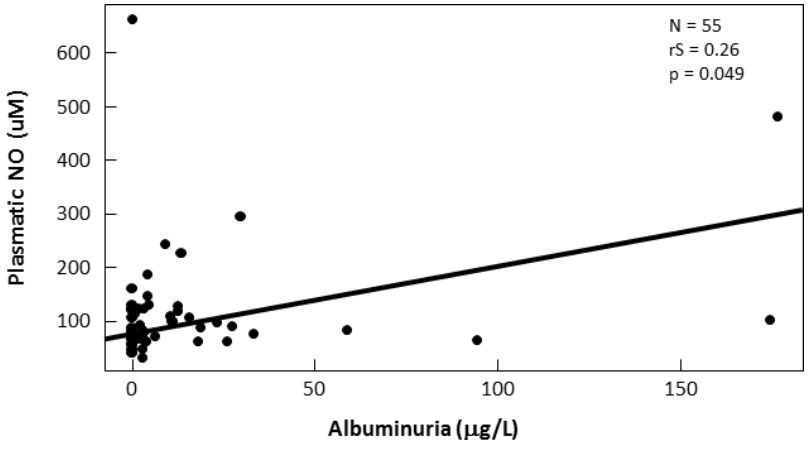

Figure 4. Correlation between plasmatic NO (μM) and albuminuria (mg/L) in T1DM.

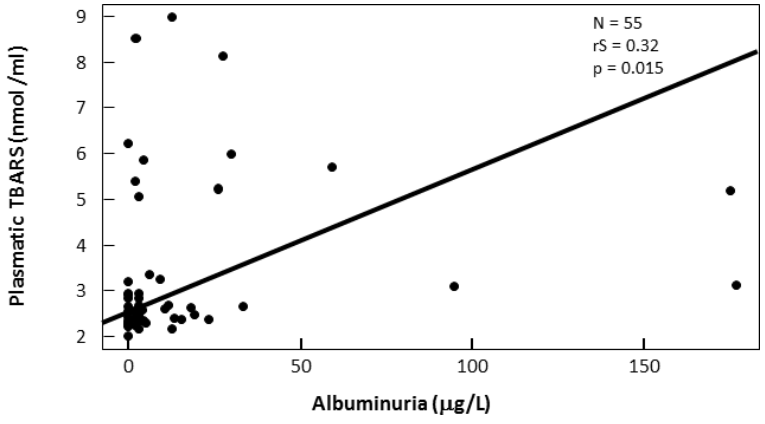

Figure 5. Correlation between plasmatic TBARS (nmol/ml) and albuminuria (mg/L) in T1DM.

dilatation in diabetic subjects and controls (16). This is also consistent with the observation that overall NO production is elevated rather than diminished in T1DM (17), what is in accordance with our data.

However, by measuring total value of plasma NO levels, it is not possible to distinguish if plasma NO levels were produced by eNOS or iNOS specifically. It has been demonstrated that high blood glucose levels inhibit endothelial production of NO (18). On the other hand, we know that hyperglycemia and oxidative stress increase iNOS activity, thereby accelerating NO synthesis (19). Other studies have found that hyperglycemia activates NF-ρχB, which induces the iNOS expression (20). Based on these data, it is reasonable to suggest that elevated NO levels in T1DM indicate increased iNOS expression and activity. Higher iNOS production of NO is in line with being a good and adaptable response to injury and inflammation. However, when NO expression is persistently up-regulated, NO is implicated in endothelial dysfunction, excessive vasodilation, extravasation and tissue injury (21). Some authors have suggested the importance of preventing excessive NO release mediated by iNOS, without suppression of eNOS in more favorable outcomes (20).

The other oxidative stress biomarker studied, 8-iso-PGF2α, in an 8-hour urine sample, showed great variability in both T1DM and controls and despite having a tendency, there was no significant difference between them. These results were like those found by other authors, who showed similar levels of this marker in controls comparing with, both T2DM treated with insulin and T1DM, but different from T2DM treated with oral medications (22). This suggests that insulin potentially exerts beneficial effects against the activation of oxidative stress dependent on sustained hyperglycemia and glycemic variability (23). So, a possible explanation for the similar levels of oxidative stress biomarkers, except plasmatic NO, in T1DM and controls in our study, is the potential inhibitory effect of the insulin therapy on oxidative stress (22). In addition, other factors that may influence the findings are the different methods for quantifying urinary 8-iso-PGF-2α (ELISA and mass spectrometry) (24) and the sample size.

Other authors found high levels of urinary 8-iso-PGF-2α in T1DM compared to healthy controls (9,15,25). Some studies have shown a correlation between this marker of oxidative stress and glycemic variability (9), while others (25,26) have not, suggesting the heterogeneity of the relationship between T1DM condition and oxidative stress biomarkers.

The results of many clinical and experimental studies have suggested that lipid peroxidation processes are activated during different stages of T1DM (27). However, in our study, plasmatic TBARS that can be considered as a lipid peroxidation index, were similar between the control group and T1DM patients with more than 5 years of disease, which was also observed by other authors (28).

Previous studies suggest that plasma lipid profile can also be affected by lipid peroxidation (27). Lower levels of antioxidant defenses can lead to higher levels of cholesterol, what could be seen in our study that found serum LDL-cholesterol and triglycerides inversely correlated with GSH/GSSG.

We found also that albuminuria was positively correlated with plasmatic NO and TBARS. This is in accordance with a study that had found elevated plasmatic TBARS levels in all albuminuric diabetic patients (29). Altered bioavailability of NO is a major contributor to endothelial dysfunction and as we known microalbuminuria may reflect a generalized vascular dysfunction (30). Taken together the plasmatic TBARS and NO levels could be also an index of initial kidney damage.

It is known that biomarkers of subclinical inflammatory response as serum CRP and ferritin have shown controversial results in T1DM patients (31,32). Mild increases of high sensitivity serum CRP are associated with a higher cardiovascular risk (33). In our study, CRP levels were significantly higher in the T1DM than in the control group, however this acute phase inflammatory protein did not correlate with oxidative stress parameters studied in this group of T1DM.

Ferritin concentration has been reported as a risk factor for the development of diabetes, impaired insulin sensitivity and cardiovascular disease (34), however in our study this parameter was similar in both controls and T1DM individuals and it did not correlate with oxidative stress parameters.

The current study has a few shortcomings. First, urinary nitric oxide was not measured, only the plasmatic sample. Also 8-iso PGF-2α was dosed in 8-hour urinary samples instead of 24-hour samples. Finally, this was a cross-sectional study, which precluded the possibility to follow up on patients and monitor the evolution of oxidative stress parameters.

The advantages of our study was the use of CGMS to calculate short term glycemic variability, which may be more important since seven point glucose measurements from SMBG, that was done in another studies, may not detect the full degree of glycemic variability.

In conclusion, young adult with T1DM had higher plasmatic NO than healthy young adults and it was, in this study, the single marker of oxidative stress correlated with glycemic variability. Plasmatic TBARS, GSH/GSSG and urinary 8-iso-PGF-2α didn't show correlation with this parameter. In addition, blood GSH/GSSG was positively correlated with lipid profile, and plasmatic NO and TBARS with albuminuria.

Therefore, the interrelationship between glycemic variability and oxidative stress markers in T1DM is heterogeneous. Lipid profile (one of cardiovascular risk component) and albuminuria (endothelial disfunction index) are associated with different oxidative stress markers during T1DM daily lives. Taken together this data collaborate to explain the different results found in the studies that searched for the correlation between glucose variability, oxidative stress and chronic diabetes consequences in T1DM. Further researches are needed, including prospective trials to better explore the long-term impact of the diabetic milieu.

Author contributions: TV was the main researcher; contributed to data collection and writing the manuscript. FV and MBBL also contributed to the data collection. GRP and MGM performed the dosage of some oxidative stress biomarkers. MALG and EMSH contributed to the discussion of the manuscript. SAD was the main coordinator of the study; contributed to study design, writing, discussion and article review.

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Consent for publication: not applicable.

Ethical approval and consent to participate: the study was approved by the Ethical Committee of Federal University of São Paulo (CAAE registration number generated in Plataforma Brazil was 02703212.6.0000.5505) and informed consent was obtained from all patients included in the study.

Disclosure: no potential conflict of interest relevant to this article was reported.

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18. Anexo VII - Outras publicações durante o mestrado

18.1. Bertoluci MC, Salles JEN, Silva-Nunes J, Pedrosa HC, Moreira RO, da Silva Duarte RMC, da Costa Carvalho DM, Trujilho FR, Dos Santos Raposo JFC, Parente EB, Valente F, de Moura FF, Hohl A, Melo M, Araujo FGP, de Araújo Principe RMMC, Kupfer R, Costa E Forti A, Valerio CM, Ferreira HJ, Duarte JMS, Saraiva JFK, Rodacki M, Castelo MHCG, Monteiro MP, Branco PQ, de Matos PMP, de Melo Pereira de Magalhães PC, Betti RTB, Réa RR, Trujilho TDG, Pinto LCF, Leitão CB. Portuguese-Brazilian evidence-based guideline on the management of hyperglycemia in type 2 diabetes mellitus. Diabetol Metab Syndr. 2020 May 24;12:45. doi: 10.1186/s13098-020-00551-1. PMID: 32489427; PMCID: PMC7245758.

Abstract

Background: In current management of type 2 diabetes (T2DM), cardiovascular and renal prevention have become important targets to be achieved. In this context, a joint panel of four endocrinology societies from Brazil and Portugal was established to develop an evidence-based guideline for treatment of hyperglycemia in T2DM.

Methods: MEDLINE (via PubMed) was searched for randomized clinical trials, meta-analyses, and observational studies related to diabetes treatment. When there was insufficient high-quality evidence, expert opinion was sought. Updated positions on treatment of T2DM patients with heart failure (HF), atherosclerotic CV disease (ASCVD), chronic kidney disease (CKD), and patients with no vascular complications were developed. The degree of recommendation and the level of evidence were determined using predefined criteria.

Results and conclusions: In non-pregnant adults, the recommended HbA1c target is below 7%. Higher levels are recommended in frail older adults and patients at higher risk of hypoglycemia. Lifestyle modification is recommended at all phases of treatment. Metformin is the first choice when HbA1c is 6.5–7.5%. When HbA1c is 7.5–9.0%, dual therapy with metformin plus an SGLT2i and/or GLP-1RA (first-line antidiabetic agents, AD1) is recommended due to cardiovascular and renal benefits. If an AD1 is unaffordable, other antidiabetic drugs (AD) may be used. Triple or quadruple therapy should be considered when HbA1c remains above target. In patients with clinical or subclinical atherosclerosis, the combination of one AD1 plus metformin is the

recommended first-line therapy to reduce cardiovascular events and improve blood glucose control. In stable heart failure with low ejection fraction (< 40%) and glomerular filtration rate (eGFR) > 30 mL/min/1.73 m2, metformin plus an SGLT-2i is recommended to reduce cardiovascular mortality and heart failure hospitalizations and improve blood glucose control. In patients with diabetes-associated chronic kidney disease (CKD) (eGFR 30–60 mL/min/1.73 m2 or eGFR 30–90 mL/min/1.73 m2 with albuminuria > 30 mg/g), the combination of metformin and an SGLT2i is recommended to attenuate loss of renal function, reduce albuminuria and improve blood glucose control. In patients with severe renal failure, insulin-based therapy is recommended to improve blood glucose control. Alternatively, GLP-1RA, DPP4i, gliclazide MR and pioglitazone may be considered to reduce albuminuria. In conclusion, the current evidence supports individualizing anti-hyperglycemic treatment for T2DM.

Keywords: Diabetes treatment, Type 2 diabetes, Cardiovascular risk, Guidelines, Heart failure, Chronic kidney disease, Ischemic heart disease, ASCVD, Atherosclerotic disease

18.2. Rassi- Cruz M, Valente F, Caniza MV. Digital therapeutics and the need for regulation: how to develop products that are innovative, patient - centric and safe. Diabetol Metab Syndr. 2022 Apr 1;14(1):48. doi: 10. 1186/s13098 -022 -00818 -9. PMID: 35365189; PMCID: PMC8972652.

Abstract

Background: Digital therapeutics are defined as therapeutic interventions that are driven by high quality software programs to prevent, manage or treat a medical disorder. These products provide great potential to improve patient outcomes, particularly for chronic disease sufferers, including people with Diabetes.

Main text: As yet, regulatory pathways for these products are rather unclear across all jurisdictions, although somewhat more progress has been made in the US and UK. Since digital therapeutics use cutting-edge technology and a logic of continuous innovation, regulation used for medical devices may not be completely appropriate. However, these products could present risks to patients if not developed and used appropriately. In the article, we consider the importance of a regulation framework and the role of self-regulation by developers as a way of ensuring patient safety while promoting innovation. We particularly emphasize the inclusion of doctors and other medical professionals in the design of the products, not only as a way of ensuring safe and effective applications, but also to encourage their take-up by patients, who tend to have high levels of trust for their HCPs.

Conclusion: Developers of digital therapeutics have the duty to create products that are safe, ethical and effective, without waiting for government regulation. Further, by self-regulating, following principles such as those provided by the Digital Therapeutics Alliance, they can develop products that serve patients better, while continuing to innovate.

Keywords: Digital therapeutics, Digital health, Regulation

18.3. Rocco ER, Mory DB, Bergamin CS, Valente F, Miranda VL, Calegare BF, Silva RQ, Dib SA. Optimal cutoff points for body mass index, waist circumference and HOMA -IR to identify a cluster of cardiometabolic abnormalities in normal glucose -tolerant Brazilian children and adolescents. Arq Bras Endocrinol Metabol. 2011 Nov;55(8):638 -45. doi: 10. 1590/s0004 -27302011000800020. PMID: 22218448.

ABSTRACT
Objective: The aim of this study was to establish the best cutoff values for waist circumference (WC), body mass index (BMI) and HOMA-IR (HR) to identify a cluster (≥ 3) of cardiovascular risk factors (CVRF) in normal glucose-tolerant (NGT) Brazilian children and adolescents.
Subjects and methods: Cross-sectional study of 319 individuals (aged 10 to 19y) from a southern Brazilian city. Gender-specific receiver-operating characteristics (ROC) curves were constructed to assess cutoffs values of BMI (kg/m2, WC (cm), and HR.
Results: The areas under the ROC curves to detect a cluster of CVRF were 0.92, 0.93 and 0.68 (females), and 0.93, 0.93 and 0.89 (males), for WC, BMI and HR, respectively. The cutoff values were 83.0 and 80.5 cm (WC), 22.7 and 20.4 kg/m2 (BMI), and 1.65 and 1.95 (HR), for females and males, respectively, to detect the cluster of CVRF.
Conclusion: These values of BMI, WC-) and (HR) detected a high proportion of NGTt Brazilian children and adolescents with a cluster of CVRF. Arq Bras Endocrinol Metab. 2011;55(8):638-45
Keywords
Children; adolescents; cardiovascular risk factor; cluster

19. Anexo VIII - Outras publicações durante o mestrado: capítulos de livros

19.1. VALENTE, O. ; VALENTE, F. . Cetoacidose Diabética e Estado Hiperglicêmico Hiperosmolar. In: Bernardo Leo Wajchenberg; Antônio Carlos Lerário; Roberto Tadeu Barcellos Betti. (Org.). Tratado de Endocrinologia Clínica. 2eded.São Paulo: AC Farmacêutica LTDA (Grupo GEN), 2014, v. , p. 483-492. Editora : GEN | Grupo Editorial Nacional; 1ª edição (21 agosto 2014)
ISBN-10: 8581141897
ISBN-13: 978-8581141893

19.2. ARBEX, A. ; ENDOCRINOLOGIA CLÍNICA NO DIA A DIA. 1. ed. Rubio, 2018. 0408p. ISBN: 9788584110605. Tratamento do DM2 - VALENTE, F. NAZATO D.

19.3. CAMARA, G. M. C.; CAMPOS, T. B. F. ; VALENTE, F. ; STRUFALDI, M. B. ; CASTILHO, S. ; ZAGURY, R. L. ; PASCALI, P. ; RODRIGUES, G. M. B. ; DUARTE, G. ; MALERBI, F. E. K. ; PECOLI, P. F. G. ; PIEPER, C. . E-book: Autocuidado e diabetes em tempos de covid-19. 2020. (Desenvolvimento de material didático ou instrucional - E-book).

19.4. ARBEX, A. ; ENDOCRINOLOGIA CLÍNICA NO DIA A DIA. 2. ed. Rubio, 2022. 0392p. ISBN: 9786588340400. Tratamento do DM2 - VALENTE, F. NAZATO D.

19.5. Filho R, Albuquerque L, Cavalcanti S, Tambascia M, Valente F, Bertoluci M. Tratamento farmacológico da hiperglicemia no DM2. Diretriz Oficial da Sociedade Brasileira de Diabetes (2022). DOI: 10.29327/557753.2022-10, ISBN: 978-65-5941-622-6.

19.6. Izar M, Fonseca F, Faludi A, Araújo D, Valente F, Bertoluci M. Manejo do risco cardiovascular: dislipidemia. Diretriz Oficial da Sociedade Brasileira de Diabetes (2022). DOI: 10.29327/557753.2022-19, ISBN: 978-65-5941-622-6.

20. Anexo IX - Trabalhos apresentados no Congresso Americano de Diabetes (ADA)

20.1. FERNANDO VALENTE, TATIANA VALENTE, SERGIO A. DIB; 2284-PUB: Overweight/Obesity in Young T1D Patients Is Differently Associated to First Degree Relatives' History or Features According to Their Gender. *Diabetes* 1 June 2020; 69 (Supplement_1): 2284–PUB. https://doi.org/10.2337/db20-2284-PUB

20.2. MARTIN CARRICA, FERNANDO VALENTE, LUCIANA MIGLIANO, YVES SEBASTIAN LORDA DUMONT, JOAO E. SALLES; 620-P: Improving Glycemic Control in Patients with T2D in Brazil through Tech-Enabled Low-Cost Virtual Monitoring. Diabetes 1 June 2020; 69 (Supplement_1): 620–P. https://doi.org/10.2337/db20-620-P