

TITLE PAGE

Is visceral fat a better predictor of the incidence of impaired glucose tolerance or type 2 diabetes mellitus than subcutaneous abdominal fat: a systematic review and meta-analysis of cohort studies. Ana Valeria Barros de Castro, MD, PhD¹, Vania S. Nunes, MD, PhD², Viorica Ionut MD, PhD³, Richard N. Bergman, PhD³, Regina El Dib, PhD⁴

1- Endocrinology Unit, Barao de Maua University Center, Medical School/ Internal Medicine Department, Endocrinology and Metabolism Unity, Medical School –Sao Paulo University, Ribeirão Preto, Sao Paulo, Brazil; 2-Endocrinology and Metabolism Unit, Internal Medicine Department, Botucatu Medical School, UNESP - Univ Estadual Paulista, São Paulo, Brazil; 3- Diabetes and Obesity Research Institute - Cedars Sinai Medical Center, Los Angeles, CA; 4- Evidence-Based Medicine Unit, Anesthesiology Department, Botucatu Medical School, UNESP - Univ Estadual Paulista, São Paulo, Brazil.

ABSTRACT

BACKGROUND: Several lines of evidence show that abdominal fat is strongly associated with insulin resistance and dysglycemia (impaired glucose tolerance - IGT or type 2 diabetes mellitus - T2DM). However, which component of abdominal fat, subcutaneous or intra-abdominal, has a major impact on the development of insulin resistance and dysglycemia is still a matter of debate. The aim of this review is to summarize the best available evidence on the contribution of subcutaneous and/or intra-abdominal adipose tissues to the incidence of impaired glucose tolerance and/or type 2 diabetes mellitus, in adults as well as to determine which type of abdominal fat is a better predictor of these metabolic disorders.

METHODS: A search of published articles on PUBMED (1966 to June 2013), EMBASE (1980 to June 2013), LILACS (1982 to June 2013) and Central Cochrane databases was conducted to identify studies evaluating the relationship between intra-abdominal and/or subcutaneous adipose tissue and the incident IGT or T2DM). Cohort studies examining the association between intra-abdominal and/or subcutaneous adipose tissue values and the prospective development of impaired glucose tolerance or type 2 diabetes mellitus (estimated risk) were included in this review. Data extraction and risk of bias assessments were performed in duplicate by 2 reviewers. Random-effects meta-analyses were performed to pool OR estimates from individual studies to assess the association between intra-abdominal and/or subcutaneous adipose tissue values at baseline and the risk of development of impaired glucose tolerance or type 2 diabetes mellitus. Statistical heterogeneity was assessed using the I^2 statistics. The risk of bias was assessed by examining the sample selected, recruitment method, completeness of follow up and blinding according to the guidelines for assessing quality in prognostic studies proposed by Hayden (29) and the MOOSE (30) statement, and adapted by us.

RESULTS: Five relevant studies were suitable for this review. The analysis showed that both VAT and abdominal SAT measurements at baseline were strong predictors of incident impaired glucose tolerance or type 2 diabetes mellitus, in minimally adjusted models. However, when other confounding variables besides age, sex and ethnicity were taken into account, VAT, but not SAT, measurements pose a high risk of the incident IGT or T2DM in a wide range of age and ethnic backgrounds (Japanese-, Hispanic-, African-Americans and Canadians).

CONCLUSIONS: In conclusion, the present results provide some evidence that VAT imposes more risk to the development of IGT and T2DM than abdominal SAT. However, more studies are necessary to confirm these results and to address the issue of changes in VAT and abdominal SAT and their predictive value regarding IGT and type 2 diabetes developments.

Correspondent author: Ana Valeria B. Castro – dra.anavaleria@gmail.com. Barao de Maua University Center, Medical School/ Internal Medicine Department, Endocrinology and Metabolism Unity, Medical School –Sao Paulo University, Ribeirão Preto, Sao Paulo, Brazil.

INTRODUCTION

Abdominal or central obesity comprises excess of visceral and subcutaneous fat depots around the abdomen. It is one of the major features associated with many, components of the metabolic syndrome, including impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM) (1-4).

Recently, two meta-analyses have shown that anthropometric measurements of abdominal adiposity, assessed by waist circumference - WC and waist circumference/height ratio - WHR) or of general obesity, assessed by body mass index-BMI, are strong predictors of T2DM incidence (5, 6). These findings were confirmed by a long-term longitudinal study in which anthropometric measurements were used as a surrogate for body fat and abdominal fat (7).

Nevertheless, the aforementioned studies, for technical reasons, could not provide further information on the weighted role of the subcutaneous and the visceral components of the abdominal fat on the risk for development of IGT and T2DM (5-11).

Several studies that applied quantitative imaging methods to assess both subcutaneous and intra-abdominal adipose tissue showed that visceral fat is more strongly correlated to metabolic risks than increased abdominal subcutaneous fat (12-24). And some authors have found that the latter is not linearly associated with the increase of metabolic abnormalities as it is observed in relation to increased intra-abdominal fat (17). They argue that increased abdominal subcutaneous fat might actually be metabolically protective in obese individual (25).

However, due to the cross-sectional and observational designs of the aforementioned studies, it is not possible to assess the relative risk of each component of the abdominal adipose tissue to the development of IGT and/or T2DM.

Addressing this issue, a few longitudinal studies showed that increased intra-abdominal adipose tissue is strongly associated with the incidence of IGT and/or T2DM (11, 26-30).

In addition, a historical cohort study that applied quantitative imaging methods to assess (dual-energy X-ray absorptiometry-DXA) confirmed the previous findings that higher amount of abdominal fat increased the risk to develop T2DM in a large cohort of Canadians women (11).

We, therefore, proposed to summarize the evidence showing the contribution of

subcutaneous and/or intra-abdominal adipose tissues to the incidence of impaired glucose tolerance and/or type 2 diabetes mellitus, in adults, through a systematic review of prospective studies. Furthermore, we aimed to determine which type of abdominal fat (i.e., subcutaneous and/or intra-abdominal) is a better predictor of the aforementioned metabolic disorders.

METHODS

Types of participants

Studies were included if participants of interest were adults (>18 years), regardless gender or ethnicity, who did not have diabetes mellitus at baseline, and were followed for at least two years until the occurrence of dysglycemia (impaired glucose tolerance and/or type 2 diabetes mellitus). Furthermore, the patients should have had measurements of visceral and/or subcutaneous adipose tissue (VAT and abdominal SAT, respectively) content values by validated abdominal imaging methodology (i.e., computerized tomography-CT, magnetic resonance imaging-MRI), expressed as continuous or categorical values or baseline means for cases (subjects who developed dysglycemia) and controls (subjects who has not developed dysglycemia).

Types of studies

This review included inception cohort studies as they have a prospective design feature over a period of time.

In order to answer the question regarding which type of abdominal fat would pose more risk to the development of IGT or T2DM, the studies should contain reports of differential odds ratio (OR) or hazard ratio (HR) for each fat type for the development of the outcome.

Types of outcome measures

The primary outcome of this review is the development of IGT and/or T2DM. The exposure was subcutaneous and/or intra-abdominal adipose tissue measurements at baseline.

Impaired fasting glucose (IFG) was defined as fasting glucose between 100 mg/dl and 199 mg/dl. Impaired glucose tolerance was defined by 2-h plasma glucose level between 140 mg/dl and 199 mg/dl after a standard oral glucose tolerance test (31). Diabetes mellitus type 2 was defined as fasting plasma glucose \geq 126 mg/dl or 2-h plasma glucose level \geq 200 mg/dl after a glucose challenge (31), as well as patient's reports or medical records informing treatment with insulin or oral antidiabetic agents during follow up.

Search strategy for identification of studies

A PUBMED (1966 to June 2013), EMBASE (1980 to June 2013), LILACS (1982 to June 2013) and Central Cochrane search of published articles was conducted to identify studies evaluating the relationship between intra-abdominal and/or subcutaneous adipose tissue and impaired glucose tolerance or type 2 diabetes mellitus. There was no language restriction. The detailed search strategy is presented in Appendix 1.

In addition, reference lists of the identified relevant studies were scrutinized for additional citations and, specialists in the field and authors of the included trials were contacted for any possible unpublished data.

Data collection and extraction

Two reviewers (AVBC and VSN) independently screened the studies identified by the literature search and extracted data. Subsequently, disagreements between the examiners were discussed between authors (AVBC and RED) to reach consensus.

Quality assessment

Clinical and imaging information that would influence the applicability and interpretation of findings and would be necessary to allow assessment of the homogeneity of studies included in this review, such as sex, age, ethnicity, duration of follow up, year of study and components of abdominal fat, were extracted.

The risk of bias was assessed by examining the sample selected, recruitment method, completeness of follow up and blinding according to the guidelines for assessing quality in prognostic studies proposed by Hayden (32) and the MOOSE (33) statement, and adapted by us. Studies were assigned as being low risk if the sample came from a population base, the follow up period was prospective and the withdrawals and drop-outs was less than 20% of the sample for each group. Studies could receive a low, high or uncertain risk of bias classification.

Data management and statistical analysis

We have presented the information in a way in which variations in similar outcomes can be examined, taking into account length of follow up, age at ascertainment and other clinically important differences such as sex, age, family history, diagnosis of IGT at baseline when the information was available. Using the available data reported, we calculated 95% confidential intervals (CI) around the odds ratio (STATA 10.1) and used Review Manager 5 software to

combine results in a forest plot using a random-effect model. Pooled odds ratio analysis was performed with STATA, v. 10.1.

Where some data was missing, attempt were made to contact authors of the primary studies. If there was no response or there was response but could not provide data, such outcomes were excluded from analysis. Studies with missing outcomes were described in characteristics of included studies table.

Investigation of heterogeneity

Heterogeneity of the studies was explored within the Chi^2 test and the I^2 statistics (32) that provide the relative amount of variance of the summary effect due to the between-study heterogeneity. We classified heterogeneity using the following I^2 values: 0 to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; and 75% to 100%: considerable heterogeneity.

If there was a substantial heterogeneity, the possible sources of heterogeneity were explored by removing studies with low methodological quality.

RESULTS

Study selection process and results from the literature search are depicted in Figure 1. In summary, we identified 6783 studies from the following database: Medline (n=3874), EMBASE (n=2715), Cochrane (Central) (n=196), Lilacs (n=198). After exclusion of duplicate records and studies that have not met our inclusion criteria, 35 studies, potentially eligible for inclusion, were requested and 19 full-text articles were selected. Following assessment of the full-text articles, five publications met all the methodological requirements and were included in this review. Detailed characteristics of the excluded and included studies are described in Tables 1 and 2. All studies received a low risk of bias.

The samples size varied from 128 (27) to 2356 (28) participants. The studies involved both young and elderly Japanese-American (11, 26, 27, 29, 30), African-American (29), Hispanic-American (29), white and black Americans (28) from both sexes.

The follow up time ranged from 5 to 11 years. Approximately 70-90% of the participants completed the study. At baseline, all participants had measurements of abdominal fat content by CT.

The outcomes were assessed by OGTT in 3 out of 5 studies (26, 27, 30) and/or by

169 medical records, self-reports or fasting glycemia ≥ 126 mg/dl (28, 29).

170 Among the participants, a total of 414/4556 subjects (9.1%) developed T2DM and 57/128
171 subjects (44.5%) developed IGT (Table 2).

172 The studies used odds ratio (OR) and the accompanying 95% confidence intervals to
173 assess the incidence of T2DM or IGT in relation to baseline measurements of VAT and
174 abdominal SAT. In one study (28), it was not possible to retrieve unavailable information about
175 the the odds ratio of SAT to predict incident T2DM. The results are summarized in Table 3.

176 Assessment of confounding factors such as age and sex was performed in all studies. The
177 inclusion of other confounding variables to the calculation of OR for the incidence of T2DM and
178 IGT such as BMI, total adiposity, insulin sensitivity, family history, IGT at baseline and others
179 varied in composite among all studies.

180 The pooled OR for dysglycemias, in relation to baseline VAT e SAT measurements, in
181 minimally adjusted models (age, sex and ethnicity), were 1.59 (CI = 1.39-1.78) e 1.48 (CI =
182 1.26-1.70), with evidence of moderate heterogeneity, $I^2 = 75\%$ (Pheterogeneity = 0.03) e 54%
183 (Pheterogeneity = 0.09); whilst in maximally adjusted models (age, sex, race, IGT, insulin
184 sensitivity, insulin secretion, fasting blood insulin, C-peptide, lipids, adipokines etc), the pooled
185 OR were 1.37 (1.15-1.58) and 0.89 (0.71-1.07), with low (34%, Pheterogeneity = 0.20) and
186 moderate heterogeneity (72%, Pheterogeneity = 0.01)

187 Insulin sensitivity and secretion were still stronger predictors of diabetes development
188 than VAT measurements when they were modeled together (29). In one of the studies, the
189 authors also showed that BMI was a strong predictor of incident T2DM in both white and black
190 subjects, but this association decreased when other confounding variables were taken into
191 account (adipokines, fasting glucose, lipids, and hypertension) and held significantly only for
192 white subjects (24). Subjects that developed T2DM presented higher indexes of general obesity
193 (BMI), VAT or abdominal SAT (Figures 2 and 3) and other characteristic of regional obesity
194 (WC, thigh fat) at baseline than those who have not (data not shown).

195 In all studies, participants that developed T2DM presented baseline values of BMI, VAT
196 and abdominal SAT or total abdominal fat significantly higher than those who did not developed

T2DM (Figures 2 and 3). Participants that developed IGT also presented higher VAT and abdominal SAT compared to those who presented normal glucose tolerance (Figures 2 and 3).

DISCUSSION

Recently, two meta-analyses have shown that anthropometric measurements of abdominal fat (i.e. WC and WHR) or general obesity (i.e. BMI) are strong predictors of the development of T2DM (5, 6), and these findings were confirmed by a long-term longitudinal study (7). The assessment of abdominal fat by direct methods also showed that increased abdominal fat is a strong predictor of both IGT and T2DM (14, 27, 30). In the present review, we also found that the group of patients who developed dysglycemia presented, at baseline assessment, higher BMI, VAT and SAT values than those who have not developed those metabolic disorders.

In addition, the present review also suggested that, adjusting for age, sex and ethnicity, both VAT and abdominal SAT measurements are strong predictors of incident dysglycemia. However, when other confounders are added to risk calculations only VAT measurements poses higher risk to the incidence of IGT or T2DM than abdominal SAT, in a wide range of age and ethnic backgrounds (Japanese-, Hispanic-, African-Americans). These results are in consonance, with a large set of studies that indicates that expanded visceral fat plays a major role in the development of insulin resistance, and ultimately of impaired glucose tolerance and type 2 diabetes mellitus (4, 34-36).

However, the issue about which component of abdominal fat pose a major impact on the relationship on the development of insulin resistance and dysglycemia is still a matter of interest and debate. Some showed that both visceral and abdominal subcutaneous fat were equally associated to the presence of insulin resistance (37, 38), whilst others showed a major role of abdominal SAT (39). In this review, it was noted that abdominal SAT, similarly to VAT is a risk factor to the development of both IGT and T2DM (OR: 1.48 x 1.59, respectively), in minimally adjusted models for confounding factors (age, sex and ethnicity). However, after adjusting to other risk factors (e.g. insulin sensitivity or secretion, adiponectin levels etc) SAT does increase the risk to the development of dysglycemia (OR: 0.89).

Although the results of this meta-analysis may highlight VAT as a stronger predictor of

IGT and T2DM than other measurements of overall and regional adiposity, they do not allow drawing conclusions regarding the direct causal role of VAT on the development of those metabolic disorders. Several attempts have been made to show a direct role of VAT in metabolic profile. In animals models, for instance, reduction of VAT, by means of the excision of the omentum, showed improvement of insulin sensitivity and glucose tolerance (40, 41). However, in morbidly obese and diabetic patients, omentectomy has not added improvement to insulin sensitivity in relation to bariatric surgery itself (42, 43). On the other hand, effective decrease of abdominal fat, especially of VAT, by proper diet, exercise and the administration of glitazones improves insulin sensitivity (44). These results suggest that there are other mechanisms involved in the association between increased abdominal fat and metabolic disorders besides the omental or visceral fat *per se*.

Several mechanisms have been proposed to explain the association between abdominal fat, particularly VAT, and metabolic disorders. It has been shown that increased VAT is associated with dysfunctional adipocytes which present higher rates of lipolysis, partly due to a higher sensitivity to adrenergic drive, which could lead to an overflow of free fatty acids (FFA) or adipokines to the liver, as well as to the muscle, compromising liver and muscle insulin sensitivity, insulin clearance and ultimately leading to the development of T2DM. Moreover, VAT is prone to inflammation which also leads to insulin resistance (45, 46). Another observation that has recently gained attention is that VAT is associated with ectopic fat deposition (liver, muscle, pancreas etc) which is also highly correlated with the development of IGT and T2DM (44, 47). In some studies, it was shown that fatty liver had a stronger association with T2DM than VAT *per se* (20, 48). These studies suggest that VAT may be a bystander in the association of regional obesity and metabolic disorders or a marker of underlying causes of disorders of insulin secretion or sensitivity such as ectopic deposition of fat in liver, muscle and pancreas.

It is interesting to note that studies have shown that the deeper part of abdominal SAT present morphological and functional characteristic similar to VAT (49), which potentially could confer this site of abdominal SAT similar influence on the risk of developing insulin resistance/dysglycemia as VAT. On the other hand, other regional SAT, such as thigh, has been reported as protective against metabolic disorders (50, 51).

Several potential limitations are present in this study. Our analyses were based on few studies which could lead to publication bias. In a considerable number of studies the diagnosis of T2DM was based in self-report or fasting glucose measurements which may result in misleading incidence of T2DM. Information about changes of VAT and abdominal SAT overtime to predict the incident of ITG and T2DM are also important to OR calculation but were not assessed in the studies. Moreover, only one study addressed the prediction of IGT (27).

In contrast, the strengths of this study are the involvement of a wide range of age and ethnic backgrounds and the feasibility to tease out the predictive values of the components of the abdominal fat (VAT and abdominal SAT) to the development of IGT and T2DM, using direct measurements of abdominal fat.

In conclusion, the present results provide some evidence that increased abdominal fat may be a significant risk factor for the development T2DM and possibly to IGT across different ethnic backgrounds and age. Our data also suggest that VAT imposes more risk to the development of dysglycemia than abdominal SAT. However, more studies are necessary to confirm these results and to address the issue of changes in VAT and abdominal SAT and their predictive value regarding IGT and type 2 diabetes developments. Studies assessing the predictive role of ectopic fat deposition (liver, muscle and pancreas) on this association are also warranted.

274 **ACKNOWLEDGEMENT**

275 We acknowledge Katrina Williams for her important suggestions to this manuscript.

Appendix 1. Search strategy for clinical question.

((Abdominal Subcutaneous Fats) OR (Abdominal Subcutaneous Fat) OR (Abdominal Subcutaneous Adipose Tissue) OR (subcutaneous fat) OR (Subcutaneous Fats) OR (Abdominal Obesities) OR (Abdominal Obesity) OR (Central Obesity) OR (Central Obesities) OR (Visceral Obesities) OR (Visceral Obesity) OR (Intra-Abdominal Fats) OR (Intra Abdominal Fat) OR (Intra-Abdominal Fat) OR (Intra-Abdominal Adipose Tissue) OR (Intra Abdominal Adipose Tissue) OR (Intra Abdominal Fat) OR (Retroperitoneal Fat) OR (Retroperitoneal Fats) OR (Retroperitoneal Adipose Tissue) OR (Visceral Fat) OR (Visceral Fats) OR (Visceral Adipose Tissue) OR (Abdominal Visceral Fat) OR (Abdominal Visceral Fats) OR (thigh fat) OR (thighs fat)) **AND** ((Impaired glucose tolerance) OR (Impaired glucose tolerances) OR (Impaired glucose tolerance) OR (Ketosis-Resistant Diabetes Mellitus) OR (Ketosis Resistant Diabetes Mellitus) OR (Ketosis-Resistant Diabetes Mellitus) OR (Maturity-Onset Diabetes Mellitus) OR (Maturity Onset Diabetes Mellitus) OR (Non Insulin Dependent Diabetes Mellitus) OR (Non-Insulin-Dependent Diabetes Mellitus) OR (Non-Insulin-Dependent Diabetes Mellitus) OR (Type 2 Diabetes Mellitus) OR (Slow Onset Diabetes Mellitus) OR (Slow-Onset Diabetes Mellitus) OR (Stable Diabetes Mellitus) OR (Type II Diabetes Mellitus) OR (Maturity Onset Diabetes Mellitus) OR MODY OR NIDT2DM OR (Adult-Onset Diabetes Mellitus) OR (Adult-Onset Diabetes Mellitus) OR (Adult Onset Diabetes Mellitus) OR (Noninsulin Dependent Diabetes Mellitus) OR (Metabolic syndrome))

276 REFERENCES

- 277 1. Despres JP, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, et al. Abdominal
278 obesity and the metabolic syndrome: contribution to global cardiometabolic risk.
279 *Arterioscler Thromb Vasc Biol.* 2008;28(6):1039-49.
- 280 2. Jensen MD. Is visceral fat involved in the pathogenesis of the metabolic syndrome?
281 Human model. *Obesity (Silver Spring).* 2006;14 Suppl 1:20S-4S.
- 282 3. Bergman RN, Kim SP, Hsu IR, Catalano KJ, Chiu JD, Kabir M, et al. Abdominal obesity:
283 role in the pathophysiology of metabolic disease and cardiovascular risk. *Am J Med.*
284 2007;120(2 Suppl 1):S3-8; discussion S29-32.
- 285 4. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the
286 metabolic syndrome. *Endocr Rev.* 2000;21(6):697-738.
- 287 5. Vazquez G, Duval S, Jacobs DR, Jr., Silventoinen K. Comparison of body mass index,
288 waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis.
289 *Epidemiol Rev.* 2007;29:115-28.
- 290 6. Freemantle N, Holmes J, Hockey A, Kumar S. How strong is the association between
291 abdominal obesity and the incidence of type 2 diabetes? *Int J Clin Pract.*
292 2008;62(9):1391-6.
- 293 7. Meisinger C, Doring A, Thorand B, Heier M, Lowel H. Body fat distribution and risk of
294 type 2 diabetes in the general population: are there differences between men and women?
295 The MONICA/KORA Augsburg cohort study. *Am J Clin Nutr.* 2006;84(3):483-9.
- 296 8. Ashwell M, Cole TJ, Dixon AK. Obesity: new insight into the anthropometric
297 classification of fat distribution shown by computed tomography. *Br Med J (Clin Res Ed).*
298 1985;290(6483):1692-4.
- 299 9. Ferland M, Despres JP, Tremblay A, Pinault S, Nadeau A, Moorjani S, et al. Assessment
300 of adipose tissue distribution by computed axial tomography in obese women: association
301 with body density and anthropometric measurements. *Br J Nutr.* 1989;61(2):139-48.
- 302 10. Irlbeck T, Massaro JM, Bamberg F, O'Donnell CJ, Hoffmann U, Fox CS. Association
303 between single-slice measurements of visceral and abdominal subcutaneous adipose
304 tissue with volumetric measurements: the Framingham Heart Study. *Int J Obes (Lond).*
305 2010;34(4):781-7.
- 306 11. Leslie WD, Ludwig SM, Morin S. Abdominal fat from spine dual-energy x-ray

- absorptiometry and risk for subsequent diabetes. *J Clin Endocrinol Metab.* 2010;95(7):3272-6.
12. Goodpaster BH, Krishnaswami S, Resnick H, Kelley DE, Haggerty C, Harris TB, et al. Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women. *Diabetes Care.* 2003;26(2):372-9.
13. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation.* 2007;116(1):39-48.
14. Bray GA, Jablonski KA, Fujimoto WY, Barrett-Connor E, Haffner S, Hanson RL, et al. Relation of central adiposity and body mass index to the development of diabetes in the Diabetes Prevention Program. *Am J Clin Nutr.* 2008;87(5):1212-8.
15. Demerath EW, Reed D, Rogers N, Sun SS, Lee M, Choh AC, et al. Visceral adiposity and its anatomical distribution as predictors of the metabolic syndrome and cardiometabolic risk factor levels. *Am J Clin Nutr.* 2008;88(5):1263-71.
16. Pigeon E, Couillard E, Tremblay A, Bouchard C, Weisnagel SJ, Joanisse DR. Mid-thigh subcutaneous adipose tissue and glucose tolerance in the Quebec family study. *Obes Facts.* 2008;1(6):310-8.
17. Porter SA, Massaro JM, Hoffmann U, Vasan RS, O'Donnel CJ, Fox CS. Abdominal subcutaneous adipose tissue: a protective fat depot? *Diabetes Care.* 2009;32(6):1068-75.
18. Liu J, Fox CS, Hickson DA, May WD, Hairston KG, Carr JJ, et al. Impact of abdominal visceral and subcutaneous adipose tissue on cardiometabolic risk factors: the Jackson Heart Study. *J Clin Endocrinol Metab.* 2010;95(12):5419-26.
19. Onat A, Ugur M, Can G, Yuksel H, Hergenc G. Visceral adipose tissue and body fat mass: predictive values for and role of gender in cardiometabolic risk among Turks. *Nutrition.* 2010;26(4):382-9.
20. Speliotes EK, Massaro JM, Hoffmann U, Vasan RS, Meigs JB, Sahani DV, et al. Fatty liver is associated with dyslipidemia and dysglycemia independent of visceral fat: the Framingham Heart Study. *Hepatology.* 2010;51(6):1979-87.
21. Smith JD, Borel AL, Nazare JA, Haffner SM, Balkau B, Ross R, et al. Visceral adipose tissue indicates the severity of cardiometabolic risk in patients with and without type 2 diabetes: results from the INSPIRE ME IAA study. *J Clin Endocrinol Metab.*

- 2012;97(5):1517-25.
22. Hanley AJ, Wagenknecht LE, Norris JM, Bergman R, Anderson A, Chen YI, et al. Adiponectin and the incidence of type 2 diabetes in Hispanics and African Americans: the IRAS Family Study. *Diabetes Care*. 2011;34(10):2231-6.
23. Indulekha K, Anjana RM, Surendar J, Mohan V. Association of visceral and subcutaneous fat with glucose intolerance, insulin resistance, adipocytokines and inflammatory markers in Asian Indians (CURES-113). *Clin Biochem*. 2011;44(4):281-7.
24. Kim S, Cho B, Lee H, Choi K, Hwang SS, Kim D, et al. Distribution of abdominal visceral and subcutaneous adipose tissue and metabolic syndrome in a Korean population. *Diabetes Care*. 2011;34(2):504-6.
25. Golan R, Shelef I, Rudich A, Gepner Y, Shemesh E, Chassidim Y, et al. Abdominal superficial subcutaneous fat: a putative distinct protective fat subdepot in type 2 diabetes. *Diabetes Care*. 2012;35(3):640-7.
26. Boyko EJ, Fujimoto WY, Leonetti DL, Newell-Morris L. Visceral adiposity and risk of type 2 diabetes: a prospective study among Japanese Americans. *Diabetes Care*. 2000;23(4):465-71.
27. Hayashi T, Boyko EJ, Leonetti DL, McNeely MJ, Newell-Morris L, Kahn SE, et al. Visceral adiposity and the risk of impaired glucose tolerance: a prospective study among Japanese Americans. *Diabetes Care*. 2003;26(3):650-5.
28. Kanaya AM, Wassel Fyr C, Vittinghoff E, Harris TB, Park SW, Goodpaster BH, et al. Adipocytokines and incident diabetes mellitus in older adults: the independent effect of plasminogen activator inhibitor 1. *Arch Intern Med*. 2006;166(3):350-6.
29. Hanley AJ, Wagenknecht LE, Norris JM, Bryer-Ash M, Chen YI, Anderson AM, et al. Insulin resistance, beta cell dysfunction and visceral adiposity as predictors of incident diabetes: the Insulin Resistance Atherosclerosis Study (IRAS) Family study. *Diabetologia*. 2009;52(10):2079-86.
30. Hoyer D, Boyko EJ, McNeely MJ, Leonetti DL, Kahn SE, Fujimoto WY. Subcutaneous thigh fat area is unrelated to risk of type 2 diabetes in a prospective study of Japanese Americans. *Diabetologia*. 2011;54(11):2795-800.
31. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2013;36 Suppl 1:S67-74.
32. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in

- systematic reviews. *Ann Intern Med.* 2006;144(6):427-37.
33. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA.* 2000;283(15):2008-12.
34. Brochu M, Starling RD, Tchernof A, Matthews DE, Garcia-Rubi E, Poehlman ET. Visceral adipose tissue is an independent correlate of glucose disposal in older obese postmenopausal women. *J Clin Endocrinol Metab.* 2000;85(7):2378-84.
35. Rendell M, Hulthen UL, Tornquist C, Groop L, Mattiasson I. Relationship between abdominal fat compartments and glucose and lipid metabolism in early postmenopausal women. *J Clin Endocrinol Metab.* 2001;86(2):744-9.
36. Hayashi T, Boyko EJ, McNeely MJ, Leonetti DL, Kahn SE, Fujimoto WY. Visceral adiposity, not abdominal subcutaneous fat area, is associated with an increase in future insulin resistance in Japanese Americans. *Diabetes.* 2008;57(5):1269-75.
37. Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE. Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. *Diabetes.* 1997;46(10):1579-85.
38. Tulloch-Reid MK, Hanson RL, Sebring NG, Reynolds JC, Premkumar A, Genovese DJ, et al. Both subcutaneous and visceral adipose tissue correlate highly with insulin resistance in african americans. *Obes Res.* 2004;12(8):1352-9.
39. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationships of generalized and regional adiposity to insulin sensitivity in men. *J Clin Invest.* 1995;96(1):88-98.
40. Lottati M, Kolka CM, Stefanovski D, Kirkman EL, Bergman RN. Greater omentectomy improves insulin sensitivity in nonobese dogs. *Obesity (Silver Spring).* 2009;17(4):674-80.
41. Xia L, Hua J, Dray X, Khashab MA, Liang S, Kim YS, et al. Endoscopic visceral fat removal as therapy for obesity and metabolic syndrome: a sham-controlled pilot study (with video). *Gastrointest Endosc.* 2011;74(3):637-44.
42. Lima MM, Pareja JC, Alegre SM, Geloneze SR, Kahn SE, Astiarraga BD, et al. Visceral fat resection in humans: effect on insulin sensitivity, beta-cell function, adipokines, and

inflammatory markers. *Obesity* (Silver Spring). 2013;21(3):E182-9.

43. Sdralis E, Argentou M, Mead N, Kehagias I, Alexandridis T, Kalfarentzos F. A prospective randomized study comparing patients with morbid obesity submitted to sleeve gastrectomy with or without omentectomy. *Obes Surg*. 2013;23(7):965-71.
44. Morelli M, Gaggini M, Daniele G, Marraccini P, Sicari R, Gastaldelli A. Ectopic fat: the true culprit linking obesity and cardiovascular disease? *Thromb Haemost*. 2013;110(4):651-60.
45. Wajchenberg BL, Giannella-Neto D, da Silva ME, Santos RF. Depot-specific hormonal characteristics of subcutaneous and visceral adipose tissue and their relation to the metabolic syndrome. *Horm Metab Res*. 2002;34(11-12):616-21.
46. Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. *Physiol Rev*. 2013;93(1):359-404.
47. Arsenault BJ, Beaumont EP, Despres JP, Larose E. Mapping body fat distribution: a key step towards the identification of the vulnerable patient? *Ann Med*. 2012;44(8):758-72.
48. Fabbrini E, Magkos F, Mohammed BS, Pietka T, Abumrad NA, Patterson BW, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. *Proc Natl Acad Sci U S A*. 2009;106(36):15430-5.
49. Walker GE, Verti B, Marzullo P, Savia G, Mencarelli M, Zurleni F, et al. Deep subcutaneous adipose tissue: a distinct abdominal adipose depot. *Obesity* (Silver Spring). 2007;15(8):1933-43.
50. McLaughlin T, Lamendola C, Liu A, Abbasi F. Preferential fat deposition in subcutaneous versus visceral depots is associated with insulin sensitivity. *J Clin Endocrinol Metab*. 2011;96(11):E1756-60.
51. Faloia E, Tirabassi G, Canibus P, Boscaro M. Protective effect of leg fat against cardiovascular risk factors in obese premenopausal women. *Nutr Metab Cardiovasc Dis*. 2009;19(1):39-44.

Fig. 1-Flowchart for identifying eligible studies

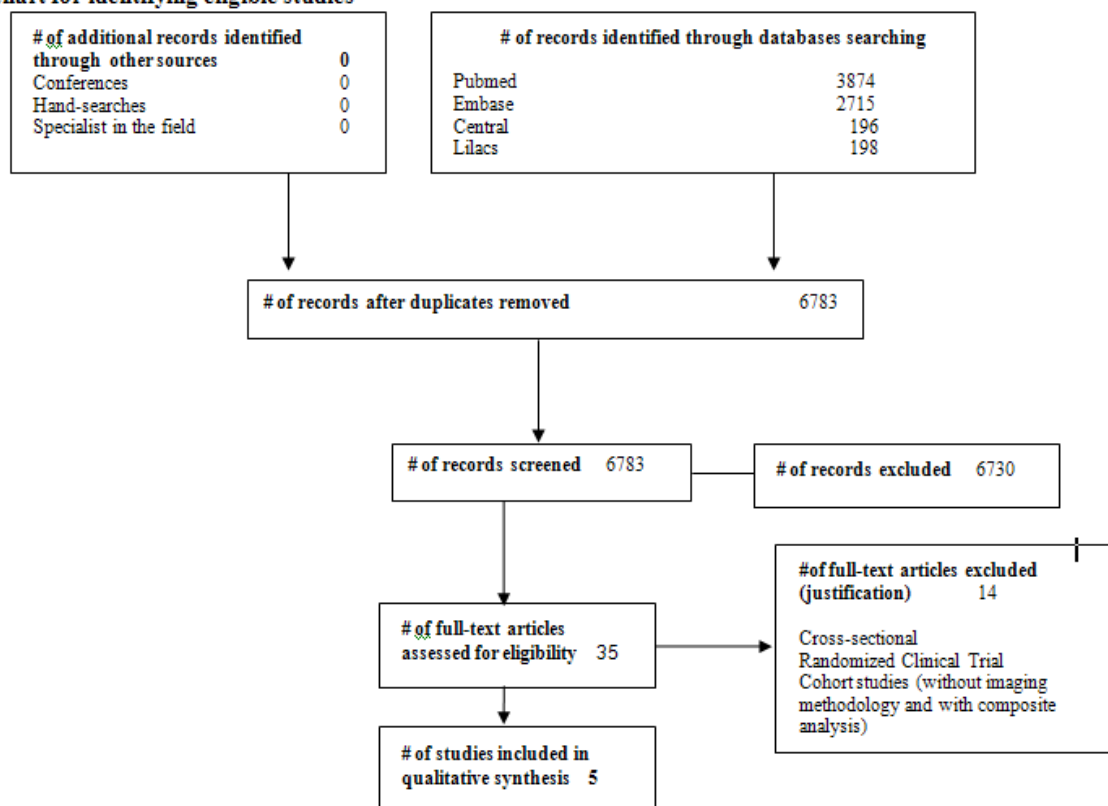


Table 1. Characteristics of the excluded studies.

| Reference | Reason for exclusion |
|---------------------------------------|--|
| Leslie WD <i>et al.</i> 2010 (11) | Historical cohort – assessment of total abdominal fat |
| Goodpaster BH <i>et al.</i> 2003 (12) | Case-control study. |
| Fox CS <i>et al.</i> 2007 (13) | Cross-sectional study. |
| Bray GA <i>et al.</i> 2008 (14) | Randomized clinical trial (placebo vs. metformin). |
| Demerath EW <i>et al.</i> 2008 (15) | Cross-sectional study; metabolic syndrome (does not separate DM2 or IGT) |
| Pigeon E <i>et al.</i> 2010 (16) | Cohort study, states glucose tolerance only |
| Porter SA <i>et al.</i> 2009 (17) | Cross-sectional study; metabolic syndrome |
| Liu J <i>et al.</i> 2010 (18) | Cross-sectional; metabolic syndrome |
| Onat A <i>et al.</i> 2010 (19) | Cohort study, outcome is a composite (DM2 and coronary heart disease) |
| Speliotes EK <i>et al.</i> 2010 (20) | Cross-sectional study |
| Smith JD <i>et al.</i> 2012 (21) | Cross-sectional study |
| Hanley AJG <i>et al.</i> 2011 (22) | Prospective study: adiponectin main outcome |
| Indulekha K <i>et al.</i> 2011 (23) | Case-control study |
| Kim S <i>et al.</i> 2011 (24) | Cross-sectional study: metabolic syndrome |

Table 2- Characteristics of the included studies.

| Citation | Design | Source of population | Ethnicity | Study size (n) | Age (mean) | Sex | Follow-up (y) | Complete follow up (%) | Exposure (Baseline VAT/SAT) | Outcome(Dysglycemia) | | Confounders (adjustment models) |
|------------------------------|------------------|--|-----------------------------|----------------|------------------------------|-----|-------------------------------|------------------------|-----------------------------|-----------------------------------|------------|--|
| | | | | | | | | | Imaging methodology | Diagnostic methodology | Number (%) | |
| Boyko EJ <i>et al</i> (26) | Inception cohort | Japanese American Community Diabetes Study (JACDS) | Japanese American | 481 | 62.2 -Nisei 41.6 - Sansei | M/F | 6 or 10 (Nisei) 6 (Sansei) | 95.2 | Abdominal TC | DM/OGTT | 78 (16.2) | Age, sex, family history (DM), VAT, SAT, non-intra-abdominal area, IGT, fasting C-Peptide, IIR |
| Hayashi T <i>et al</i> (27) | Inception cohort | JACDS | Japanese American | 128 | 39.5 | M/F | 10-11 | 92.1 | Abdominal TC | IGT/OGTT | 57 (44.5) | Age, sex, VAT, BMI, HOMA-IR, IIR, FPG, VAT +FPG, IIR+FPG |
| Kanaya AM <i>et al</i> (28) | Inception cohort | The Health, Aging, and Body Composition (Health ABC) Study | Black/white | 2356 | 73.5 | M/F | 5 | 97.8 | Abdominal TC | DM/medical record | 143 (6.1) | Age, sex, ethnicity, adipokines, FPG, insulin, HDL-C, TG, BP |
| Hanley AJG <i>et al</i> (29) | Inception cohort | The Insulin Resistance Atherosclerosis Study (IRAS) Family Study | African-, Hispanic-American | 1230 | 46.3 | M/F | 5 | 77 | Abdominal TC | DM/ self-report, fasting glycemia | 90 (7.3) | Age, sex, ethnicity, SI, HOMA IR, AIRg, IFG, TG, HDL-C, sBP |
| Hoyer D <i>et al</i> (30) | Inception cohort | JACDS | Japanese American | 489 | 52.2 | M/F | 10 | 94 | Abdominal TC | DM/OGTT | 103 (21.1) | Age, sex, family history (DM), BMI, STF, VAT, SAT |

JACDS-Japanese American Community Diabetes Study; dysglycemia – impaired glucose tolerance (ITG) and diabetes mellitus (DM); OGTT – oral glucose tolerance test, CT – computerized tomography; VAT – visceral adipose tissue; SAT – subcutaneous adipose tissue; IIR – Index of insulin resistance; IR-insulin resistance, FPG- fasting plasma glucose; TG – triglyceride; sBP- systolic blood pressure; STF – subcutaneous total fat

Table 3 - Pooled odds ratio (OR) to the incidence of of dysglycemia (IGT and/or T2DM) in relation to baseline values of VAT or SAT
(Assessed by computerized tomography)

| MINIMALLY ADJUSTED MODELS ¹ | | | | | | |
|--|-------------|------------------|---|-------------|------------------|---|
| | VAT | | | SAT | | |
| STUDY | OR | 95% CI | WEIGHT (%) | OR | 95% CI | WEIGHT (%) |
| Boyko EJ <i>et al</i> (26) | 2.40 | 1.50-3.85 | 2.75 | 1.35 | 0.95-2.05 | 16.14 |
| Hayashi T <i>et al</i> (27) | 1.52 | 1.06-2.19 | 11.88 | 1.63 | 1.10-2.39 | 11.92 |
| Kanaya AM <i>et al</i> (28)* | 1.33 | 1.10-1.60 | 60.66 | - | - | - |
| Hanley AJG <i>et al</i> (29) | 2.65 | 1.97-3.56 | 6.00 | 2.06 | 1.60-2.65 | 17.71 |
| Hoyer D <i>et al</i> (30) | 2.00 | 1.60-2.50 | 18.72 | 1.30 | 1.00-1.60 | 54.24 |
| POOLED | 1.59 | 1.39-1.78 | Heterogeneity p=0.03*; I²=75% | 1.48 | 1.26-1.70 | Heterogeneity p=0.09; I²=54% |
| MAXIMALLY ADJUSTED MODELS ² | | | | | | |
| STUDY | OR | 95% CI | WEIGHT (%) | OR | 95% CI | WEIGHT (%) |
| Boyko EJ <i>et al</i> (26) | 2.15 | 1.30-3.60 | 3.44 | 0.70 | 0.50-1.00 | 51.16 |
| Hayashi T <i>et al</i> (27) | 2.48 | 1.09-5.25 | 1.05 | 1.23 | 0.69-2.17 | 5.84 |
| Kanaya AM <i>et al</i> (28) | 1.19 | 0.95-1.49 | 62.49 | - | - | - |
| Hanley AJG <i>et al</i> (29) | 1.68 | 1.22-2.33 | 14.79 | 1.49 | 1.12-1.99 | 16.90 |
| Hoyer D <i>et al</i> (30) | 1.50 | 1.10-2.10 | 18.22 | 0.80 | 0.50-1.20 | 26.10 |
| POOLED | 1.37 | 1.15-1.58 | Heterogeneity p=0.20; I²=34% | 0.89 | 0.71-1.07 | Heterogeneity p=0.01*; I²=72% |

1-age, sex and race; 2- 1+ IGT, insulin sensitivity, insulin secretion, fasting blood insulin, C-peptide, lipids, adipokines etc * information unavailable

Fig. 2 - Relative differences of baseline visceral adipose tissue (VAT) (cm²) values from patients who developed dysglycemia (Type 2 Diabetes mellitus or impaired glucose tolerance) or not.

Visceral adipose tissue

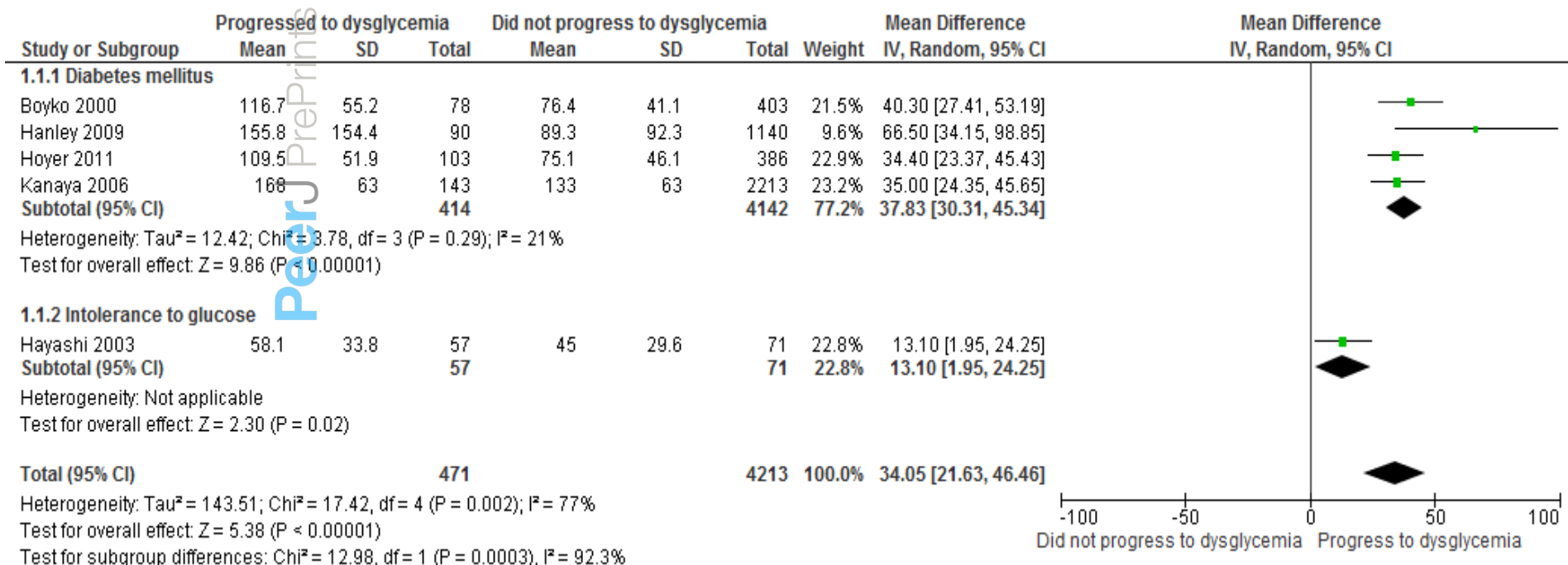


Fig. 3 - Relative differences of baseline abdominal subcutaneous adipose tissue (SAT) values (cm²) from patients who developed dysglycemia (Type 2 Diabetes mellitus or impaired glucose tolerance) or not.

Abdominal subcutaneous adipose tissue

