Title

Can increased visceral adiposity without body weight changes accelerate carotid atherosclerosis in South Korean participants with type 2 diabetes?

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Title: Can increased visceral adiposity without body weight changes accelerate carotid atherosclerosis in South Korean participants with type 2 diabetes?

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Keywords: carotid atherosclerosis, carotid intima-media thickness, obesity, Type 2 diabetes mellitus, visceral fat thickness

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Abstract: Aims: Type 2 diabetes mellitus (T2DM) and visceral obesity are associated with each other and with cardiovascular diseases. We determined whether increased visceral adiposity without weight gain was associated with sex-specific accelerated carotid atherosclerosis in South Koreans with T2DM.
Methods: From 2003 to 2012, we recruited 280 participants with T2DM for the Seoul Metabolic Syndrome cohort who had body weight, visceral fat thickness (VFT), and carotid intima-media thickness (CIMT) measured at intervals of 2 years. According to VFT change, sex-specific quartiles of clinical characteristics and changes of CIMT were determined. Logistic regression models predicted the odds of the progression of CIMTs in each quartile.
Results: During 2 years of observation, VFTs fell by 5.2±13.5 mm in men ($P<0.001$) and 3.4±10.5 mm in women ($P<0.001$). Progression of IMT was only significant for women's maximal IMT (0.031±0.145 mm, $P=0.012$), while significant improvements in HbA1c were found (0.9%; $P<0.001$ in both sexes). There were no significant differences in clinical characteristics, or in progression of carotid IMT in men or women according to 2-year quartiles of VFT change.
Conclusions: Our results do not suggest that increased visceral adiposity without body weight changes impacts the CIMT progression in South Korean men or women with T2DM.

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June 8, 2015

Vivian Fonseca, MD
Editor-in-Chief, *Journal of Diabetes and Its Complications*

Re: Can increased visceral adiposity without body weight changes accelerate carotid atherosclerosis in South Korean participants with type 2 diabetes? [Ms. Ref. No.: JDC-D-15-00139R1]

Dear Dr. Fonseca:

Thank you for the opportunity to revise again, based on the helpful critique of Reviewer 1. Please see our specific responses to reviewers' comments below.

Reviewer #1: In this study, they have reported that visceral obesity leads to atherosclerosis. Ultrasonography is a noninvasive, cost-effective method to assess visceral obesity. Visceral fat change without weight change had little effect on atherosclerosis. Despite the advantages, use of sonography for assessment of body composition is accompanied by important disadvantages. Sonography entails use of equipment and is significantly more expensive than simple assessment of anthropometric features. Although the value of sonography has been shown in most studies, sporadic reports question the strong association between sonographic findings and those of standard techniques [1] and clinical outcome [2]. There is also an evident need for objective and accurate indexes such as intraabdominal fat thickness, abdominal wall fat index, preperitoneal fat, minimum subcutaneous fat thickness, mesenteric fat thickness and preperitoneal circumference that can be applied to special patient groups. Furthermore, adequate examiner training is demanded as a precondition for reliable and reproducible measurements. Once these issues are resolved, it is highly plausible that sonography will be used in clinical practice for the routine assessment of regional adiposity. Therefore in my opinion regional adiposity can be assessed with anthropometric data and imaging techniques. The former include waist-to-hip ratio, waist circumference, and abdominal sagittal diameter.
A fully automated individualized analyses method is now possible and may, given a long term sequantial database, lead to an individual predictability that was not previously available. Moreover, when the intima-media thickness was measured the identities of subjects were not literally hidden from the observer as this not possible in this study. Thus, I wonder how different the results would have been if the automated individualized analyses method that are more accurate had been used to measure thickness in these cases.

1.Stevens-Simon C, Thureen P, Stamm E, Scherzinger A. A comparison of four techniques for measuring central adiposity in postpartum adolescents. J Matern Fetal Med 2001; 10:209-213.
2.Chaowalit N, Somers VK, Pellikka PA, Rihal CS, Lopez-Jimenez F. Subepicardial adipose tissue and the presence and severity of coronary artery disease. Atherosclerosis 2006; 186:354-359.

Response: Thank you for your valuable comment. We agree that VFT measurement by ultrasonography may not be accurate as a measure of visceral adiposity in some particular groups. Therefore, we inserted a statement of this limitation of our study in the Discussion section (p. 11, paragraph 4). Moreover we agree that technical aspects concerning the reproducibility of serial within-individual changes may be a problem in this study. Thus, we think we would have more accurate results if the automated individualized analyses method had been used to measure CIMT in our cases. However, measurement variability of our study was acceptable.

In addition to this revision in response to Reviewer 1, we also made minor edits for clarity in the Discussion, e.g.:

p. 10, paragraph 1: Mean CIMT increment of our participants was only 0.0045 mm per year under HbA1c level of 8.6% (70 mmol/mol), and it was just about 13% of that of usual T2DM patients among control groups from the 8 studies in which mean HbA1c was 7.86%[21].

p. 11, paragraph 2: Overall glycemic control was revealed to be the most important factor in determining the progression of carotid atherosclerosis in participants with T2DM with increased visceral adiposity without body weight gain through 2 years. This finding indicates that blood glucose control may play the principal role in interventions to inhibit a progression of CIMT.

Again, thank you for the opportunity to submit a revision for re-consideration for publication. We hope the revision adequately addresses the reviewer's concern and that the paper is now acceptable for publication.

Sincerely,

Elizabeth Barrett-Connor, MD

***Highlights (for review)**

- Visceral obesity leads to atherosclerosis.
- Ultrasonography is a noninvasive, cost-effective method to assess visceral obesity.
- Visceral fat change without weight change had little effect on atherosclerosis.

Can increased visceral adiposity without body weight changes accelerate carotid atherosclerosis in South Korean participants with type 2 diabetes?

Running title: Visceral fat without weight changes & atherosclerosis

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Abstract

Aims: Type 2 diabetes mellitus (T2DM) and visceral obesity are associated with each other and with cardiovascular diseases. We determined whether increased visceral adiposity without weight gain was associated with sex-specific accelerated carotid atherosclerosis in South Koreans with T2DM.

Methods: From 2003 to 2012, we recruited 280 participants with T2DM for the Seoul Metabolic Syndrome cohort who had body weight, visceral fat thickness (VFT), and carotid intima-media thickness (CIMT) measured at intervals of 2 years. According to VFT change, sex-specific quartiles of clinical characteristics and changes of CIMT were determined. Logistic regression models predicted the odds of the progression of CIMTs in each quartile.

Results: During 2 years of observation, VFTs fell by 5.2±13.5 mm in men (P<0.001) and 3.4±10.5 mm in women (P<0.001). Progression of IMT was only significant for women's maximal IMT (0.031±0.145 mm, P=0.012), while significant improvements in HbA1c were found (0.9%; P<0.001 in both sexes). There were no significant differences in clinical characteristics, or in progression of carotid IMT in men or women according to 2-year quartiles of VFT change.

Conclusions: Our results do not suggest that increased visceral adiposity without body weight changes impacts the CIMT progression in South Korean men or women with T2DM.

Key Words: carotid atherosclerosis, carotid intima-media thickness, obesity, Type 2 diabetes mellitus, visceral fat thickness

1. Introduction

Obesity can cause many serious medical illnesses that impair the quality of life and often lead to increased morbidity and premature death [1]. Recently, South Korea has undergone rapid economic, social, and cultural changes, including nutrition transformations resulting in obesity that may result in a hugely increased burden of chronic diseases [2]. Obesity and Type 2 diabetes mellitus (T2DM) are intimately associated in terms of pathophysiology, and constitute high risk for coronary artery disease, cerebrovascular disease, and peripheral vascular disease, reflecting accelerated arteriosclerosis [3].

Obesity, estimated by body mass index (BMI), cannot be the sole indicator of increased metabolic diseases; many research studies support the idea that visceral fat, unlike subcutaneous fat, plays an essential role in metabolic disease development [4]. Many prospective studies have confirmed that visceral fat leads to insulin resistance, and is closely associated with hypertension and dyslipidemia, which enhance atherosclerosis [4-6]. T2DM patients are at especially high risk for cardiovascular diseases and visceral obesity. Therefore early reliable estimates of visceral adiposity and atherosclerotic disease risks are potentially very important for T2DM patients.

The amount of visceral fat can be evaluated accurately with computed tomography (CT) and magnetic resonance imaging (MRI) [7]. However, both techniques have limitations: radiation exposure for CT and cost-effectiveness for MRI. As an alternative, ultrasonography (US) is a noninvasive, accurate, reproducible, and cost-effective method to assess visceral fat accumulation [8]. High visceral fat measured by US has been closely associated with an increased risk of cardiovascular diseases (CVD) [9]. Moreover, it has been reported that visceral fat measured by US has a similar accuracy compared to CT [10]. Carotid intima-media thickness (CIMT) is a surrogate marker for CVD [11]used in both research and clinical settings.

Reduction of body weight and especially visceral fat is a key consideration for improving CVD risk among abdominally obese patients. However, it is unclear whether increased visceral adiposity without weight change can accelerate carotid atherosclerosis. In this study we aimed to determine whether increased visceral adiposity without weight gain accelerated carotid

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atherosclerosis over 2 years in participants who had known T2DM at baseline.

2. Materials and Methods

2.1 Subjects

As a part of the Seoul Metabolic Syndrome cohort, 9,532 participants were consecutively enrolled at the Huh's Diabetes Center in Seoul, Korea from 2003 to 2012. This cohort included 423 participants with known T2DM who had body weight, visceral fat thickness (VFT) and CIMT measurements at intervals of 2 years (±3 months) at least once from 2003 to 2012; 280 of these participants with stable body weight over that interval were enrolled in this study (Fig. 1). Using our most recent data, we defined stable body weight as a weight change of less than 5% of initial body weight through 2 years, because changes of 5% or greater are considered clinically relevant [12]. Exclusion criteria were type 1 diabetes; history of clinical coronary artery disease or cerebral or peripheral vascular disease; renal dysfunction (defined as blood creatinine level ≥ 2.0 mg/dl); hepatic dysfunction (defined as alanine aminotransferase and/or aspartate aminotransferase blood level ≥3×the upper normal laboratory limit); use of glucocorticoid medications; pregnancy; other serious diseases such as cancer, infection, Cushing's syndrome, acromegaly, or any other disorder likely to alter glycemia; hypercholesterolemia, hypothyroidism or hyperthyroidism; use of any hormone medications; alcoholism or drug abuse. The protocol was approved by the Institutional Review Board/Ethics Committee of Hallym University Sacred Heart hospital. Informed written consent was obtained from each participant.

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Height and weight were measured with each participant wearing light clothing and no shoes. Waist circumference was determined at the midpoint between the lower rib and the iliac crest. All participants had measurements for fasting plasma glucose, HbA1c, C-peptide, insulin, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. The participants completed a questionnaire concerning history of diseases and smoking status. Body fat percentage was evaluated by a bioelectrical impedance analysis method (Inbody 4.0, Biospace Co. Ltd, Seoul,

Korea).

2.2. Visceral Fat Thickness (VFT)

Using a 3.5-MHz convex probe (LOGIQ 7, GE, Milwaukee, WI, USA), we performed US in participants when they were in the supine position to assess visceral adiposity. Procedures were done after the participants had fasted at least 4 h. Transverse scanning was performed to measure visceral fat thickness 1 cm above the umbilicus. The probe was placed as lightly as possible with the skin to avoid disfiguring the abdominal cavity. Images were collected immediately after expiration to reduce the influence of the respiration. VFT was defined as the distance between the anterior wall of the aorta and the internal face of the rectus abdominis muscle vertical to the aorta. The intra-observational coefficient of variation (CV) was 1.5- 2.0%.

2.3. CIMT

CIMT was measured by a single examiner using a B-mode ultrasound with a 10-MHz linear probe (LOGIQ 7, GE, Milwaukee, WI). CIMT was measured at three points of the common carotid artery 1 cm proximal to the bifurcation, and the mean value of six measurements from the right and left carotid arteries was used. When reproducibility was tested, the day-to-day coefficient of variation was 4.5% for CIMT measurements. When calcifications or plaques showed heterogeneity in the area of CIMT determination, measurements were performed proximally in order to exclude plaques. Change in CIMT was defined as ΔCIMT (CIMT after 2 year - CIMT at study entry); any CIMT change >0 mm over 2 years indicated disease progression [13].

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2.4. Insulin resistance

Insulin resistance was assessed by the short insulin tolerance test (SITT) as a rate constant for

plasma glucose disappearance (*Kitt*: %/min) [14]. The SITT was carried out early in the morning after an overnight fast. Venous blood samples were collected as per protocol at 0, 3, 6, 9, 12, and 15 min after an intravenous bolus injection of prediluted regular insulin (Humulin, Eli Lilly, Indianapolis, IN) at a dose of 0.1 units/kg, as per protocol. Plasma glucose concentrations were determined immediately after sampling using a Beckman glucose analyzer II (Beckman Instruments, Fullerton, CA), and then the *Kitt* was calculated from the slope of the fall in log-transformed plasma glucose between 3 and 15 min. Immediately after the test, 100 mL of 20% dextrose solution was administered intravenously to prevent potential hypoglycemia.

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2.5 Statistics

Continuous variables were reported as mean±SD, and categorical factors were reported as percentages. Paired *t*-test was used to compare participants between baseline and after 2 years. Quartiles of various clinical characteristics according to visceral fat thickness change for 2 years were determined stratifying by sex. The intergroup comparisons were performed using a one-way ANOVA test followed by a Scheffé post hoc test and chi-square test as appropriate. Comparisons of CIMTs were adjusted by general linear model using the covariates of age, duration of diabetes, smoking status, hypoglycemic agents, antihypertensive treatment, lipid-lowering agents, systolic blood pressure, *Kitt*, HDL cholesterol, LDL cholesterol, triglyceride, HbA1c, and baseline VFT. Inclusion of covariates in the general linear model removed their contribution to change in mean and maximal CIMTs. Comparisons of the prevalence of the progression of carotid atherosclerosis were made by chi-square test. To estimate the odds ratio (OR) of the progression of carotid atherosclerosis in each quartile, logistic regression was performed, and the lowest quartile was used as the reference category. Multivariate-adjusted OR is shown with 95% CIs. Four models examining the association of anthropometric indices and CIMT were used under different adjustment schemes. The first model adjusted only for age. The second model additionally adjusted for duration of diabetes, smoking status, hypoglycemic medications (insulin, sulfonylureas, metformin, α-glucosidase inhibitors, and thiazolidinediones), antihypertensive treatment (calcium channel blocker, angiotensin receptor blocker, ACE

inhibitor, and β-blocker), lipid-lowering agents (statins and fibrates), systolic blood pressure, *Kitt*, HDL cholesterol, LDL cholesterol, and triglyceride levels. The third model additionally adjusted for HbA1c, and the fourth model additionally adjusted for baseline VFT.

In order to evaluate factors that influence the progression of CIMT, multiple regression analyses were performed. We selected the variables that had a potential association with the progression of CIMT and known cardiovascular risk factors [age, duration of diabetes, BMI, waist circumference, smoking status, antidiabetic treatments (insulin, sulfonylurea, metformin, α-glucosidase inhibitors, and thiazolidinediones), antihypertensive treatments (calcium channel blocker, angiotensin II receptor blocker, and ACE inhibitor), lipid-lowering drugs (statins and fibrates), systolic blood pressure, *Kitt*, HDL cholesterol, LDL cholesterol, triglycerides, and HbA1c].

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The PASW version 18.0 software (IBM Co., Armonk, NY, USA) was used for statistical analyses. $P<0.05$ was considered significant.

3. Results

3.1. Clinical characteristics of participants

Baseline characteristics of the 280 participants are shown in Table 1; 50.7% (N=142) were women. The mean age was 57.3±10.1 years, and the mean duration of known T2DM was 7.1±7.0 years. Among oral anti-diabetic drugs sulfonylureas and metformin were most commonly used. About 36% of participants were treated for hypertension; the most commonly used anti-hypertensive medication in both men and women was an angiotensin receptor blocker. About 32% had dyslipidemia, predominantly treated with statins. The proportion of active smokers was 28.3% in men; no women were active smokers. Baseline BMI, waist circumference, and VFT were near the reported Asian or South Korean normal range, as reported [10, 15].

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As shown in Table 2, after 2 years, waist circumferences were reduced in both men and women by about 5 cm (both $P<0.001$). With the reduction of waist circumference, VFTs were reduced by

5.2 ±13.5 mm in men (P<0.001) and 3.4 ±10.5 mm in women (P<0.001). Body fat percentages were also reduced in both men (from 22.6 to 21.4%, P=0.010) and women (from 28.8 to 27.4%, P=0.015). The progression of CIMTs was not significant except women's maximal CIMT (0.031±0.145 mm, P=0.012) after 2 years. Over 2 years there were significant improvements on HbA1c (by 0.9%, 9.8 mmol/mol, P<0.001 in both men and women).

3.2. Clinical characteristics according to quartiles of VFT change for 2 years

In both men and women, the higher the baseline VFT, the more VFT decreased over 2 years. Moreover, VFTs were markedly reduced by more than 30% compared to baseline values in the lowest quartile (Q1) group in both sexes. On the other hand, in the highest quartile (Q4) group, VFTs increased by about 20% compared to baseline in both men and women, with no significant differences in clinical characteristics according to quartiles of VFT change for 2 years in men or women. HbA1c level of the Q1 group was higher by 1.2% (13.1 mmol/mol) than that of men in the Q4 group with no significant differences. There were no significant differences in clinical characteristics in men or women according to 2 year quartiles of VFT change (Table 3).

3.3. Progression of CIMT according to quartiles of VFT change for 2 years

There were no significant differences in progression of mean and maximal CIMT according to quartiles of VFT change for 2 years in both men and women (Table 4).

3.4. Multiple regression analyses of the progression of CIMT

HbA1c was found to be an independent predictor of the progression of mean (β=0.275, P=0.043) and maximal (β=0.278, P=0.035) CIMT in men. Moreover, HbA1c (β=0.314, P=0.034) was an independent risk factor for the progression of mean ~~CIMT in~~CIMT in women; HbA1c (β=0.332, P=0.037) and age (β=0.313, P=0.038) were found to be independent predictors of the progression of maximal CIMT in women.

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4. Discussion

It is well-known that obesity increases the risk of cardiovascular disease [16], and that risk of cardiovascular disease varies with the distribution of body fat. Visceral fat is strongly related to the development of cardiovascular diseases [17] and, generally, an increase in visceral fat is accompanied by overall weight gain. In some cases visceral fat can be increased without overall weight gain. Changes in cardiovascular risks in this context could be very interesting.

Weight loss studies have shown that visceral fat loss is related to cardiometabolic improvement [18, 19]. Recently, Rittig *et al*. [20] demonstrated that only visceral fat loss and not body weight loss or total fat loss was associated with improvement in endothelial function in T2DM-prone participants who were involved in a 9-month lifestyle intervention. However, in our 2 year study, there were no significant differences in the progression of CIMT regardless of the amount of visceral fat changes in participants with T2DM who had no noteworthy weight change.

There may be several reasons why we did not find significant differences in carotid atherosclerosis associated with change in visceral fat. First, the participants included in this study were relatively healthy T2DM patients with low cardiovascular risk, and without history of cardiovascular diseases. They had limited lipid and blood pressure problems, nearly normal BMI and visceral adiposity at baseline, and maintained stable body weight through 2 years. Another reason why we did not find significant CIMT changes according to VFT differences was probably because at least one-third of participants (33.9%) were taking various cardiovascular medications (statin, RAS inhibitor, calcium channel blocker, thiazolidinedione), which could decrease or inhibit the progression of CIMT. In addition, ~~reduction of~~ their glucose control state assessed by HbA1c was reduced from 8.6% (70 mmol/mol) to 7.7% (61 mmol/mol); HbA1c is known as a major risk factor for the progression of carotid atherosclerosis, which may explain why we did not find differences of CIMT progression according to quartiles of VFT change. Another possible reason for finding no demonstrable differences is that participants' medication compliance was quite good and the participants did well in regular hospital checkups, even though carotid US and VFT examination are uninsured tests and expensive in South Korea. The

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progression of CIMT in our participants was very low compared to those of control groups from 8 other studies [21]. In these 8 other studies, annual progression of CIMT was approximately 0.034 mm under HbA1c level of 7.86% (62 mmol/mol). Mean CIMT increment of our participants was only 0.0045 mm per year under HbA1c level of 8.6% (70 mmol/mol), and it was just about 13% of that of usual T2DM patients among control groups from the 8 studies in which mean HbA1c was 7.86%~~under a little better glucose control state~~ [21]. The progression of CIMT was too small to show any significant differences according to 2-year quartiles of VFT change.

In this study, mean VFT decreased by 9.3% over two years, and traditional cardiovascular risk factors, such as blood glucose and cholesterol levels, were improved. Despite the improvement in cardiovascular risk factors during this period, maximal CIMT increased by only 0.03 mm. This may be because age is a powerful determinant for the progression of CIMT [21]. Although there was marked visceral fat reduction (>30% of baseline) in the lowest quartile group in both sexes, CIMTs were not reduced. One possible reason is that baseline VFT of this group was highest in both men and women; therefore their baseline cardiovascular risks could have been relatively high. In contrast, in the highest quartile, baseline VFT was lowest in both men and women. In this study, those with highest VFT at baseline had the most VFT loss or negative change, whereas those with the lowest VFT at baseline had increased VFT over time. Participants with highest VFT at baseline might have had stricter life style modification. Although CIMT is associated with atherosclerosis, thickening CIMT may not be entirely due to atherosclerosis. Intimal thickening is a complex process, depending on various factors, including blood pressure, local hemodynamics, and shear stress [22]. It is possible that CIMT change is not a good surrogate marker to estimate cardiovascular risk in patients with T2DM. Usefulness of measuring CIMT over time is disputed, and large meta-analyses have reported that change in CIMT is not predictive of cardiovascular events [22, 23], despite the strong association between single CIMT measurement and cardiovascular disease [24, 25]. It should be noted that general obesity itself is an important risk factor for carotid atherosclerosis; and changes of visceral obesity without significant weight changes could have little effect on the progression of carotid atherosclerosis [26]. Moreover, the possible protective role of subcutaneous fat against subclinical atherosclerosis, which was not measured in our study, might have affected our results~~.~~

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[27]. Finally, current obesity, rather than its duration, may be the most important precursor of clinical cardiovascular and metabolic outcomes [28].

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O~~In this study, o~~verall glycemic control was revealed to be the most important factor in determining the progression of carotid atherosclerosis in participants with T2DM with increased visceral adiposity without body weight gain through 2 years. This finding indicates that blood glucose control may play the principal role in interventions to inhibit a progression of CIMT.

In this study, although the significance and relative weighting of cardiovascular risk factors were different, there were no significant differences between women and men. The prevalence of dyslipidemia was approximately above 30% in both sexes in our study. The prescription rate of statins (11.6% in men, 14.5% in women, respectively) falls below the prevalence of dyslipidemia. However, these prescription rates in participants with T2DM are comparable with those presented in a South Korean nationwide study from 1998 to 2010 [29]~~[29]~~.

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Participants were not randomly selected and the study was not designed prospectively~~—~~two limitations of our study. ~~and drawn from a small sample.~~ It should also be noted that VFT measurement by ultrasonography may not be accurate as a measure of visceral adiposity in some selected populations[30, 31]--another limitation. Moreover, methods used to maintain (within ±5%) baseline body weight for a 2-year period were not described in this study. Actually, changes of VFT and carotid CIMT might considerably differ depending on whether participants maintained their weight through regular exercise and diet control or not. We also could not examine whether there was any redistribution of abdominal fat from visceral to subcutaneous. However, body fat percentages were significantly reduced in our study; therefore we believe there was a large increase in subcutaneous fat amount in the participants. ~~Moreover, the present~~Our study also has a limitation in that the number of subjects was small~~. Therefore~~; this limitation~~, it can~~ precludes drawing of firm conclusions.

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~~The~~ A ~~significance~~ strength of our study is that it is the first ~~published~~ study of cardiovascular risk changes according to change of visceral adiposity in South Korean T2DM patients who had stable weight over time. Moreover, all CIMT examinations were performed by a single examiner

in our study;. Considering considering inter-observer variability in the CIMT examination, this is an important strength of our study. In addition, Oour cohort included a large number of participants with diabetes or metabolic syndrome, participants who periodically had a detailed survey and many tests related to cardiovascular complications.

In conclusion, our results suggest that increased visceral adiposity without body weight changes is not associated with the progression of atherosclerosis in South Korean patients with T2DM. Longer studies are needed to define early detection of cardiovascular risks in patients with T2DM.

5. Acknowledgements

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Figures and Tables

Figure 1. Study population framework. CVD, cardiovascular disease; VFT, visceral fat thickness; CIMT, carotid intima–media thickness.

Table 1 – Baseline clinical characteristics of participants (N = 280)

	Total	Men (N=138)	Women (N=142)
Age (year)	57.3±10.1	55.2±11.3	59.4±8.2
DM duration (year)	7.1±7.0	6.5±7.2	7.7±6.7
Antihyperglycemic agents (%)			
Insulin	10.0	8.0	12.0
Sulfonylureas	48.0	43.5	52.1
Metformin	40.5	36.2	44.4
α-Glucosidase inhibitors	9.3	6.5	12.0
Thiazolidinediones	7.9	8.0	7.7
Hypertension (%)	35.5	30.4	40.1
Antihypertensive treatment (%)			
CCB	8.6	8.7	8.5
ACEi	6.1	7.2	4.9
ARB	15.8	10.9	20.4
Dyslipidemia (%)	31.5	30.4	32.4
Lipid-lowering treatment (%)			
Statins	13.3	11.6	14.8
Fibrates	6.5	5.8	7.0
Active smoker (%)	16.2	28.3	0.0
BMI (kg/m^2)	23.6±4.6	21.5±2.6	25.7±5.2
Weight (kg)	63.1±10.4	62.7±8.1	63.5±12.4
Waist (cm)	83.6±10.2	84.4±8.7	82.8±11.4
VFT (mm)	46.1±18.4	50.8±20.0	41.5±15.5
Body fat (%)	25.7±4.4	22.6±3.9	28.8±4.8

SBP (mmHg)	133.2±17.0	131.5±17.5	134.8±16.5
DBP (mmHg)	84.4±11.4	84.7±11.7	84.1±11.2
Kitt (%/min)	2.0±0.9	2.0±1.0	2.0±0.9
mean CIMT (mm)	0.848±0.160	0.840±0.152	0.856±0.168
maximal CIMT (mm)	0.939±0.184	0.932±0.170	0.946±0.197
HbA1c (%)	8.6±2.0	8.6±2.1	8.6±1.9
HbA1c (mmol/mol)	70±22	70±23	70±21
Total Cholesterol (mmol/l)	5.1±1.1	5.0±1.1	5.2±1.0
Triglyceride (mmol/l)	1.8±1.1	1.7±1.1	1.8±1.1
HDLc (mmol/l)	1.3±0.2	1.3±0.4	1.3±0.4
LDLc (mmol/l)	2.9±0.9	2.9±0.9	2.9±0.8

Data are means±SD, unless otherwise noted. DM, diabetes mellitus; CCB, calcium channel blockers; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; VFT, visceral fat thickness; SBP, systolic blood pressure; DBP, diastolic blood pressure; CIMT, carotid intima media thickness; HDLc, high density lipoprotein cholesterol; LDLc, low density lipoprotein cholesterol

Table 2 – Clinical characteristics of participants in baseline and 2 years later

	Baseline	2 years later	*P*
Men (N=138)			
BMI (kg/m^2)	21.5±2.6	21.1±2.5	0.185
Weight (kg)	62.7±8.1	61.7±8.2	0.040
Waist (cm)	84.4±8.7	79.7±8.5	<0.001
VFT (mm)	50.8±20.0	45.5±17.7	<0.001
Body fat (%)	22.6±3.9	21.4±3.8	0.010
SBP (mmHg)	131.5±17.5	132.9±16.8	0.498
DBP (mmHg)	84.7±11.7	85.0±10.3	0.821
mean CIMT (mm)	0.840±0.152	0.853±0.155	0.225
maximal CIMT (mm)	0.932±0.170	0.954±0.166	0.059
HbA1c (%)	8.6±2.1	7.7±1.7	<0.001
HbA1c (mmol/mol)	70±23	57±19	<0.001
Total Cholesterol (mmol/l)	5.0±1.1	4.8±1.0	0.115
Triglyceride (mmol/l)	1.7±1.1	2.0±1.8	0.096
HDLc (mmol/l)	1.3±0.4	1.3±0.3	0.349
LDLc (mmol/l)	2.9±0.9	2.7±0.9	0.069
Women (N=142)			
BMI (kg/m^2)	25.7±5.2	25.5±5.1	0.747
Weight (kg)	63.5±12.4	62.9±11.7	0.675
Waist (cm)	82.8±11.4	77.9±10.7	<0.001
VFT (mm)	41.5±15.5	38.1±14.6	<0.001
Body fat (%)	28.8±4.8	27.4±4.8	0.015
SBP (mmHg)	134.8±16.5	135.8±12.2	0.572
DBP (mmHg)	84.1±11.2	85.4±10.3	0.310
mean CIMT (mm)	0.856±0.168	0.861±0.174	0.608
maximal CIMT (mm)	0.946±0.197	0.977±0.205	0.012
HbA1c (%)	8.6±1.9	7.7±1.5	<0.001
HbA1c (mmol/mol)	70±21	63±16	<0.001
Total Cholesterol (mmol/l)	5.2±1.0	5.0±1.0	0.178
Triglyceride (mmol/l)	1.8±1.1	1.8±1.3	0.322
HDLc (mmol/l)	1.3±0.4	1.4±0.3	0.758
LDLc (mmol/l)	2.9±0.8	2.8±0.9	0.398

Data are means±SD. BMI, body mass index; VFT, visceral fat thickness; SBP, systolic blood pressure; DBP, diastolic blood pressure; CIMT, carotid intima media thickness; HDLc, high density lipoprotein cholesterol; LDLc, low density lipoprotein cholesterol

Table 3. Baseline clinical characteristics according to quartiles (Q) of visceral fat thickness change for 2 years

	Q1	Q2	Q3	Q4	*P*
Men (N=138)					
Number	34	35	34	35	0.085
Changes of VFT (mm)[1]	-21.4±13.4 mm	-8.4±2.4 mm	-0.1±2.1 mm	9.3±5.6 mm	<0.001
Age (year)	58.5±10.4	53.5±11.3	56.6±11.3	52.2±11.7	0.085
DM duration (year)	5.5±5.4	6.9±7.5	8.3±8.8	5.3±6.7	0.309
~~Antihyperglycemic agents (%)~~					
~~Insulin~~	~~5.9~~	~~8.6~~	~~8.8~~	~~8.6~~	~~0.966~~
~~Sulfonylureas~~	~~41.2~~	~~48.6~~	~~47.1~~	~~37.1~~	~~0.755~~
~~Metformin~~	~~35.3~~	~~40.0~~	~~35.3~~	~~34.3~~	~~0.960~~
~~α-Glucosidase inhibitors~~	~~14.7~~	~~2.9~~	~~2.9~~	~~5.7~~	~~0.154~~
~~Thiazolidinediones~~	~~2.9~~	~~8.6~~	~~14.7~~	~~5.7~~	~~0.316~~
Hypertension (%)	38.2	42.9	17.6	22.9	0.069
~~Antihypertensive treatment (%)~~					
~~CCB~~	~~8.8~~	~~8.6~~	~~8.8~~	~~8.6~~	~~1.000~~
~~ACEi~~	~~2.9~~	~~2.9~~	~~17.6~~	~~5.7~~	~~0.057~~
~~ARB~~	~~11.8~~	~~14.3~~	~~11.8~~	~~5.7~~	~~0.697~~
Dyslipidemia (%)	38.2	28.6	29.4	25.7	0.701
~~Lipid-lowering treatment (%)~~					
~~Statins~~	~~11.8~~	~~17.1~~	~~17.6~~	~~0.0~~	~~0.077~~
~~Fibrates~~	~~2.9~~	~~8.6~~	~~8.8~~	~~2.9~~	~~0.547~~
Active smoker (%)	17.6	28.6	32.4	34.3	0.298
BMI (kg/m^2)	20.9±1.6	23.4±2.9	23.0±2.4	20.1±3.1	0.087
Weight (kg)	59.8±6.0	68.3±7.0	67.1±5.5	59.4±10.6	0.109
Weight after 2 year (kg)	59.0±5.8	65.3±7.6	66.4±4.9	59.0±11.9	0.202

Waist (cm)	83.8±9.4	85.3±8.1	84.7±9.7	84.0±8.2	0.914
VFT (mm)	63.7±20.0[2,3]	54.3±18.0	42.2±17.6	43.1±16.9	<0.001
Body fat (%)	23.2±4.0	23.3±3.9	22.3±3.8	21.6±3.8	0.079
SBP (mmHg)	135.3±18.4	133.9±17.0	129.3±17.6	127.2±16.3	0.170
DBP (mmHg)	83.3±12.4	87.4±10.8	81.4±11.5	86.6±11.7	0.112
Kitt (%/min)	2.0±1.0	2.2±1.1	2.0±0.8	1.9±1.0	0.619
mean CIMT (mm)	0.831±0.132	0.810±0.135	0.865±0.191	0.853±0.143	0.446
maximal CIMT (mm)	0.920±0.151	0.907±0.125	0.955±0.247	0.944±0.137	0.636
HbA1c (%)	8.0±1.6	8.3±2.0	9.0±2.6	9.2±2.0	0.067
HbA1c (mmol/mol)	64±18	67±22	75±28	77±22	0.067
Total Cholesterol (mmol/l)	5.0±1.0	4.9±1.0	4.8±0.8	5.5±1.5	0.058
Triglyceride (mmol/l)	1.9±0.9	1.8±1.2	1.8±1.1	1.6±1.0	0.739
HDLc (mmol/l)	1.2±0.2	1.2±0.2	1.3±0.5	1.3±0.4	0.287
LDLc (mmol/l)	2.8±0.9	2.8±1.0	2.8±0.7	3.2±1.1	0.434
Women (N=142)					
Number	36	35	36	35	
Changes of VFT (mm)[1]	-16.7±7.4	-5.9±2.1	0.3±1.6	8.9±5.4	<0.001
Age (year)	56.5±7.8	60.5±8.3	60.8±7.7	59.7±8.5	0.094
DM duration (year)	9.3±8.0	7.7±6.3	7.4±6.9	6.2±5.3	0.291
~~Antihyperglycemic agents (%)~~					
~~Insulin~~	~~11.1~~	~~14.3~~	~~11.1~~	~~11.4~~	~~0.973~~
~~Sulfonylureas~~	~~58.3~~	~~45.7~~	~~50.0~~	~~54.3~~	~~0.709~~
~~Metformin~~	~~58.3~~	~~40.0~~	~~36.1~~	~~42.9~~	~~0.251~~
~~α-Glucosidase inhibitors~~	~~13.9~~	~~14.3~~	~~13.9~~	~~5.7~~	~~0.656~~
~~Thiazolidinediones~~	~~8.3~~	~~8.6~~	~~8.3~~	~~5.7~~	~~0.972~~

Hypertension (%)	38.9	57.1	33.3	31.4	0.123
~~Antihypertensive treatment (%)~~					
~~CCB~~	~~5.6~~	~~14.3~~	~~5.6~~	~~8.6~~	~~0.510~~
~~ACEi~~	~~5.6~~	~~5.7~~	~~5.6~~	~~2.9~~	~~0.942~~
~~ARB~~	~~27.8~~	~~25.7~~	~~11.1~~	~~17.1~~	~~0.277~~
Dyslipidemia (%)	33.3	37.1	30.6	28.6	0.905
~~Lipid-lowering treatment (%)~~					
~~Statins~~	~~25.0~~	~~14.3~~	~~8.3~~	~~11.4~~	~~0.222~~
~~Fibrates~~	~~13.9~~	~~5.7~~	~~8.3~~	~~0.0~~	~~0.151~~
Active smoker (%)	0.0	0.0	0.0	0.0	-
BMI (kg/m^2)	24.2±3.4	27.2±4.7	25.1±8.3	25.0±5.2	0.770
Weight (kg)	56.3±3.8	68.6±10.5	63.0±20.8	61.2±7.9	0.437
Weight after 2 year (kg)	58.7±2.1	67.0±8.4	63.3±20.6	59.8±8.3	0.567
Waist (cm)	84.1±9.2	83.3±7.1	84.4±10.3	79.1±16.8	0.226
VFT (mm)	52.7±14.3[2,3,4]	43.1±14.9	33.1±12.0	37.1±13.7	<0.001
Body fat (%)	28.3±5.0	29.9±4.9	29.3±4.9	27.8±4.7	0.108
SBP (mmHg)	131.4±17.0	138.4±17.2	134.2±15.4	135.3±16.1	0.357
DBP (mmHg)	81.7±9.6	85.4±11.9	84.7±9.7	84.5±13.3	0.520
Kitt (%/min)	1.8±0.8	2.0±1.0	2.2±1.0	1.8±0.8	0.145
mean CIMT (mm)	0.862±0.127	0.838±0.178	0.875±0.194	0.848±0.171	0.803
maximal CIMT (mm)	0.920±0.206	0.933±0.194	0.980±0.200	0.949±0.192	0.603
HbA1c (%)	8.5±1.9	8.5±1.6	8.8±2.2	8.6±1.9	0.873
HbA1c (mmol/mol)	69±21	69±18	73±24	70±21	0.873
Total Cholesterol (mmol/l)	5.1±0.9	5.2±1.0	5.1±1.1	5.2±1.1	0.924
Triglyceride (mmol/l)	2.0±1.3	1.8±1.1	1.4±0.7	1.8±1.3	0.169

HDLc (mmol/l)	1.3±0.3	1.3±0.3	1.4±0.4	1.3±0.4	0.896
LDLc (mmol/l)	2.9±0.8	2.9±0.8	2.9±0.8	2.6±0.7	0.549

Q1 was the lowest quartile. Data are means±SD, unless otherwise noted. VFT, visceral fat thickness; DM, diabetes mellitus; CCB, calcium channel blockers; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CIMT, carotid intima media thickness; HDLc, high density lipoprotein cholesterol; LDLc, low density lipoprotein cholesterol. [1] $P < 0.001$ between all groups; [2] $P<0.001$, Q1vs. Q3; [3] $P<0.001$ Q1 vs. Q4; [4] $P<0.05$, Q1 vs. Q2

Table 4 - Progression of CIMT according to quartiles (Q) of visceral fat thickness change for 2 years

	Q1	Q2	Q3	Q4	*P*
Men (N=138)					
Number	34	35	34	35	
progression of mean CIMT (mean±SD)					
Unadjusted (mm)	0.012±0.134	0.007±0.124	0.008±0.154	0.027±0.109	0.914
Adjusted (mm)[1]	0.012±0.134	0.007±0.124	0.008±0.154	0.027±0.109	0.884
Adjusted (mm)[2]	0.025±0.147	0.019±0.110	-0.041±0.141	0.026±0.092	0.131
Adjusted (mm)[3]	0.025±0.147	0.019±0.110	-0.048±0.139	0.026±0.092	0.074
Adjusted (mm)[4]	0.025±0.147	0.019±0.110	-0.048±0.139	0.026±0.092	0.077
progression of mean CIMT (yes)					
Unadjusted (%)	50.0	60.0	64.7	54.3	0.629
Adjusted OR (95% CI)[1]	1	1.534 (0.583-4.032)	1.849 (0.697-4.904)	1.221 (0.465-3.207)	
Adjusted OR (95% CI)[2]	1	1.588 (0.357-7.068)	0.509 (0.094-2.754)	0.788 (0.161-3.848)	
Adjusted OR (95% CI)[3]	1	1.627 (0.358-7.386)	0.522 (0.095-2.877)	0.828 (0.159-4.325)	
Adjusted OR (95% CI)[4]	1	1.539 (0.334-7.098)	0.424 (0.068-2.649)	0.636 (0.101-3.968)	
progression of maximal CIMT (mean±SD)					
Unadjusted (mm)	0.018±0.147	0.021±0.105	0.011±0.178	0.038±0.112	0.866
Adjusted (mm)[1]	0.018±0.147	0.021±0.105	0.011±0.178	0.038±0.112	0.843
Adjusted (mm)[2]	0.028±0.162	0.037±0.096	-0.028±0.183	0.031±0.095	0.320
Adjusted (mm)[3]	0.028±0.162	0.037±0.096	-0.040±0.176	0.031±0.095	0.129
Adjusted (mm)[4]	0.028±0.162	0.037±0.096	-0.040±0. 176	0.031±0.095	0.167
progression of maximal CIMT (yes)					
Unadjusted (%)	52.9	54.3	61.8	54.3	0.881
Adjusted OR (95% CI)[1]	1	1.047 (0.401-2.730)	1.431 (0.544-3.765)	1.044 (0.398-2.743)	
Adjusted OR (95% CI)[2]	1	2.924 (0.606-14.111)	1.149 (0.231-5.728)	0.866 (0.184-4.069)	

Adjusted OR (95% CI)[3]	1	2.747 (0.566-13.335)	0.997 (0.194-5.129)	0.730 (0.145-3.681)	
Adjusted OR (95% CI)[4]	1	2.371 (0.476-11.815)	0.634 (0.103-3.885)	0.413 (0.063-2.732)	
Women (N=142)					
Number	36	35	36	35	
progression of mean CIMT (mean±SD)					
Unadjusted (mm)	0.016±0.117	0.008±0.109	0.000±0.108	-0.004±0.147	0.900
Adjusted (mm)[1]	0.016±0.117	0.008±0.109	0.000±0.108	-0.004±0.147	0.673
Adjusted (mm)[2]	0.008±0.109	0.021±0.114	-0.001±0.115	0.010±0.101	0.692
Adjusted (mm)[3]	0.008±0.109	0.025±0.114	-0.001±0.115	0.006±0.102	0.589
Adjusted (mm)[4]	0.008±0.109	0.025±0.114	-0.001±0.115	0.006±0.102	0.584
progression of mean CIMT (yes)					
Unadjusted (%)	52.8	65.7	55.6	57.1	0.717
Adjusted OR (95% CI)[1]	1	1.528 (0.576-4.052)	0.980 (0.379-2.537)	1.082 (0.417-2.806)	
Adjusted OR (95% CI)[2]	1	2.633 (0.738-9.394)	1.033 (0.284-3.760)	1.983 (0.460-8.552)	
Adjusted OR (95% CI)[3]	1	2.982 (0.795-11.177)	0.940 (0.243-3.630)	1.850 (0.426-8.038)	
Adjusted OR (95% CI)[4]	1	3.423 (0.812-14.428)	1.117 (0.243-5.139)	2.101 (0.442-9.992)	
progression of maximal CIMT (mean±SD)					
Unadjusted (mm)	0.055±0.173	0.015±0.133	0.027±0.137	0.026±0.139	0.703
Adjusted (mm)[1]	0.055±0.173	0.015±0.133	0.027±0.137	0.026±0.139	0.613
Adjusted (mm)[2]	0.080±0.177	0.029±0.138	0.030±0.110	0.042±0.078	0.388
Adjusted (mm)[3]	0.080±0.177	0.025±0.139	0.030±0.110	0.049±0.074	0.442
Adjusted (mm)[4]	0.080±0.177	0.025±0.139	0.030±0.110	0.049±0.074	0.474
progression of maximal CIMT (yes)					
Unadjusted (%)	69.4	62.9	61.1	57.1	0.759
Adjusted OR (95% CI)[1]	1	0.668 (0.244-1.830)	0.614 (0.226-1.669)	0.535 (0.198-1.446)	
Adjusted OR (95% CI)[2]	1	0.697 (0.196-2.486)	0.904 (0.235-3.471)	0.533 (0.123-2.305)	
Adjusted OR (95% CI)[3]	1	0.631 (0.173-2.299)	0.854 (0.209-3.483)	0.620 (0.139-2.760)	

Adjusted OR (95% CI)[4]	1	0.764 (0.184-3.174)	1.082 (0.220-5.317)	0.743 (0.150-3.675)

Q1 was the lowest quartile. CIMT, carotid intima media thickness; VFT, visceral fat thickness.[1]Adjusted for age; [2]Like 1 and additionally adjusted for duration of diabetes, smoking status, hypoglycemic agents (insulin, sulfonylurea, metformin, α-glucosidase inhibitors, and thiazolidinediones), antihypertensive treatments (calcium channel blocker, angiotensin II receptor blocker, and ACE inhibitor), lipid-lowering drugs (statins and fibrates), systolic blood pressure, *Kitt*, HDL cholesterol, LDL cholesterol, and triglyceride; [3]Like 2 and additionally adjusted for HbA1c; [4]Like 3 and additionally adjusted for baseline VFT.

Figure

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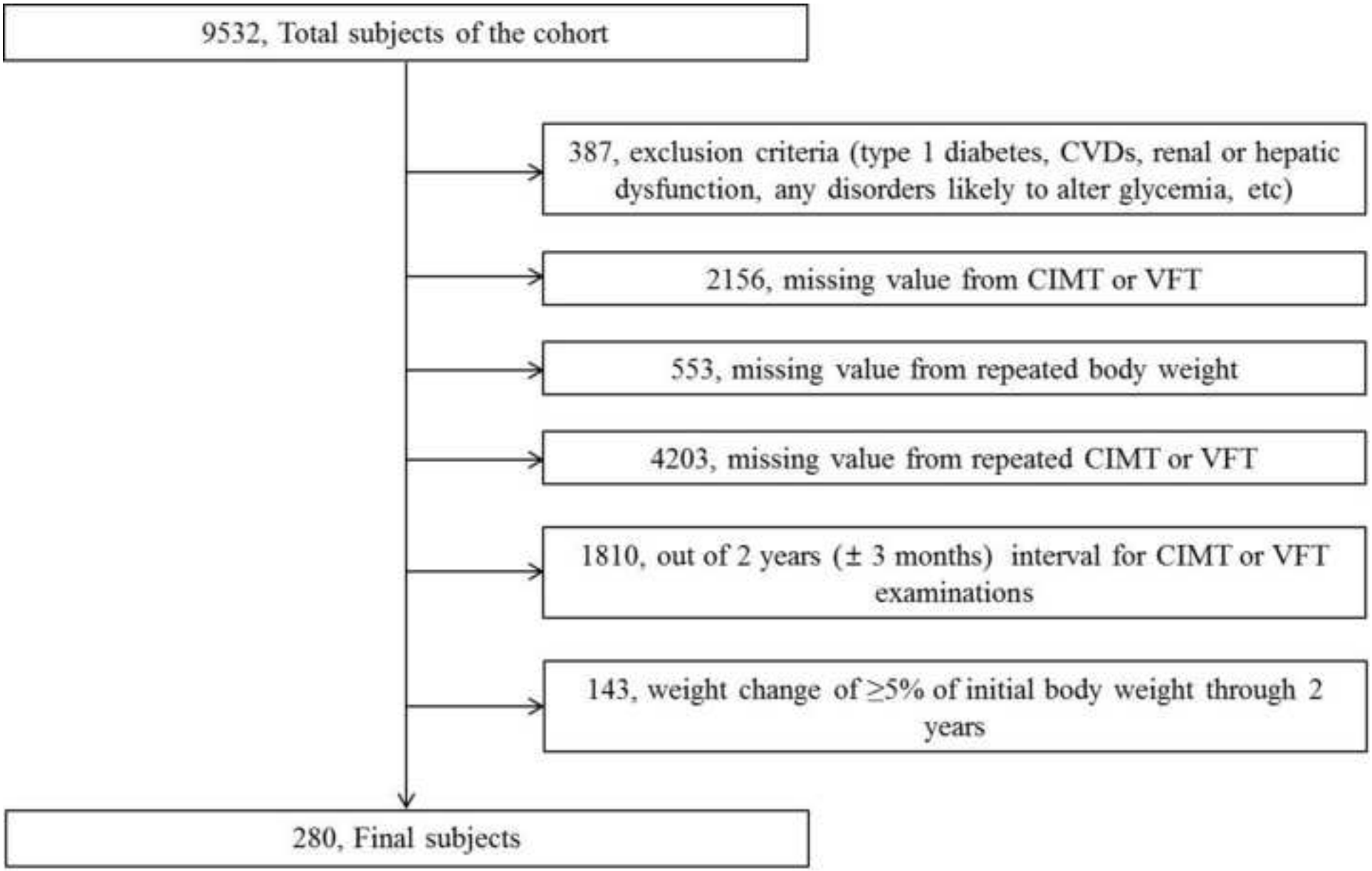

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