Dysregulated lipid storage and its relationship with insulin resistance and cardiovascular risk factors in non-obese Asian patients with type 2 diabetes

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ABSTRACT
The prevalence of non-obese type 2 diabetes in Asians is up to 50%. This review aims to summarize the role of regional fat in the development of insulin resistance and cardiovascular risk in non-obese Asian type 2 diabetes as well as the role of intra-pancreatic fat and β-cell dysfunction. The body fat content of non-obese Asian type 2 diabetic patients is not different from that of non-diabetic subjects but the proportion of intra-abdominal and intra-hepatic fat are greater. Visceral fat contributes to insulin resistance and cardiovascular risk in non-obese Asian type 2 diabetes. Intra-hepatic fat and the hypertrophic abdominal subcutaneous adipocytes are associated with insulin resistance and cardiovascular risk in non-obese, non-diabetic Asian subjects. It may be true in non-obese Asian type 2 diabetic patients. The role of intra-myocellular lipid and insulin resistance is uncertain. Intra-pancreatic fat may not be involved in β-cell dysfunction in non-obese Asian type 2 diabetes.

KEYWORDS
type 2 diabetes; non-obese; subcutaneous fat; abdominal subcutaneous fat; visceral fat; intra-hepatic fat; intra-myocellular lipid; intra-pancreatic fat

It is known that a significant number of type 2 diabetic patients particularly in Asian regions are not obese [1–4]. Up to 50% of Asian type 2 diabetic patients have BMI <25 kg/m² [5]. These non-obese diabetic subjects have lower insulin sensitivity and lower insulin secretion than non-diabetic subjects as similarly observed in obese diabetic counterparts [6–8]. Abdominal obesity, as defined by waist circumference >90 cm for men and >80 cm for women, has been demonstrated to play a major role in the development of insulin resistance of type 2 diabetes in Asian populations [5,9]. However, most of the studies are from obese subjects, the study of the relationships of total or regional adiposity to insulin resistance and metabolic abnormalities specifically in non-obese patients are relatively few. Furthermore, since structural and biochemical characteristics of subcutaneous and visceral fats are not similar between non-obese and obese subjects [10], it is possible that such relationships may be different between non-obese and obese type 2 diabetes. The purpose of this review is to summarize the latest evidence from English language literature about the role of regional adipose tissues which include subcutaneous, visceral or intra-abdominal, intra-hepatic and intra-myocellular fat in the development of insulin resistance and the increase of cardiovascular risk factors in non-obese Asian patients with type 2 diabetes. The role of intra-pancreatic fat and β cell dysfunction in non-obese Asian patients is also reviewed. The term “diabetes” in this review denotes type 2 diabetes and BMI < 25 kg/m² is used as a definition of non-obesity in Asian population throughout this review.

Role of differentially distributed adiposity in non-obese Asian type 2 diabetic patients

Visceral or intra-abdominal fat
It is known that despite lower amount of total fat mass, Asian populations tend to accumulate visceral fat greater than other ethnicities even in subjects with lower BMI ranges [11]. Non-obese Asian diabetic patients have been shown to have greater visceral fat mass than BMI-matched, non-diabetic subjects with no difference of total body fat. The study by Jang et al [12] in 26 non-obese, Korean diabetic men demonstrated that diabetic men had significantly greater waist-hip ratio and visceral fat areas by CT than age- and BMI-matched non-diabetic men. Two case-control studies in non-obese Indian and Chinese diabetic men and women confirmed those findings from Korean study [13,14]. Jung et al [15] studied 1,603 non-obese Korean subjects and reported visceral fat mass had stronger association with diabetes...
than other anthropometric measures in both men and women. The longitudinal follow-up study of second generation Japanese-American men and women indicated that the amount of visceral fat was a strong predictor of progression to diabetes [16]. Subjects who started with greater amount of visceral fat are more likely to develop diabetes. There was no difference of BMI or the amount of total body fat between those who did or did not progress to diabetes. Kim et al [17] also demonstrated that increased waist-to-height ratio or waist circumference was better than BMI in prediction of diabetes in the next 5 years in non-obese, non-diabetic Korean subjects.

The direct study of the relationship of visceral fat and insulin resistance in non-obese Asian diabetic population is scarce. Our studies in non-obese, diabetic and non-diabetic Thai women indicated that the amount of visceral fat was higher in diabetic women and visceral fat, not total body fat, was strongly associated with insulin resistance measured by clamp method in diabetic women [18,19]. Visceral fat was also associated with increased blood pressure, fasting insulin and uric acid levels in non-obese diabetic women. However the relationship of visceral fat and insulin resistance could not be observed in non-obese, non-diabetic women [19]. The population-based study from the 4th Thailand National Health Examination Survey in 2008–2009 by Aekplakorn et al (Aekplakorn W, personal communication) confirmed the higher prevalence of abdominal obesity, hypertension, high triglyceride and low HDL cholesterol levels in non-obese diabetic Thai subjects than those of healthy controls. Likewise, the study in 93 non-obese Asian Indian men and women with type 2 diabetes indicated that visceral fat but not abdominal subcutaneous fat was positively associated with insulin resistance, tumor necrosis factor-alpha (TNF-α) and highly sensitive C-reactive protein levels as well as carotid intimal media thickness [20]. Visceral fat, not abdominal subcutaneous fat, was associated with systolic and diastolic blood pressure, glucose and lipid levels in non-obese, non-diabetic and pre-diabetic Chinese adults [21]. The positive dose-response relationships of visceral fat and the prevalence of metabolic syndrome has been reported in non-obese, non-diabetic Japanese subjects [22]. This is possibly true in non-obese diabetic subjects. Fukuda et al [23] reported increased systemic arteriosclerosis measured by ultrasonography and lower adiponectin levels in non-obese Japanese diabetic patients who had visceral fat accumulation compared with those without. Reduction of visceral fat, independent of body weight or abdominal subcutaneous fat, resulted in lowered triglyceride and increased HDL cholesterol levels in 1,106 non-obese, non-diabetic Japanese men [24].

The existing evidence strongly support the role of visceral or intra-abdominal fat in the development of insulin resistance and cardiometabolic risk in non-obese Asian type 2 diabetic patients.

**Subcutaneous fat**

In general, adipose tissues of healthy subjects have preadipocytes or adipose stem cells residing in stromal vascular fraction which can accommodate positive energy balance in the form of triglyceride. These cells respond to surplus energy through processes of proliferation or expansion so called adipocyte hyperplasia or adipocyte hypertrophy, respectively. Preadipocytes of subcutaneous adipose tissue replicate and differentiate into mature adipocytes (adipocyte hyperplasia) more efficiently than those of visceral depot [25]. The mature adipocyte has its maximum capacity for expansion which is determined by genetic, gender or certain hormones [25–27]. The study by Sato et al [28] in non-diabetic Japanese adults indicates that the maximum storage capacity of abdominal subcutaneous fat occurs at BMI of 23–24 kg/m² in women and 24–25 kg/m² in men. Once the adipocyte expansion limit is reached, lipid cannot be stored further and spilled over to other adipose and non-adipose tissues [29–31]. The significant correlation of visceral fat mass and abdominal subcutaneous adipocyte size observed in Tchoukalova et al study in non-diabetic Caucasian population supports this notion [32]. However, the adipocyte capacity to store lipid has inter-depot difference. With positive energy balance, the adipocytes of gluteofemoral depot shows a proliferative responses whereas those of abdominal subcutaneous depot has adipocyte hypertrophy [33,34]. Hence the gluteofemoral depot can accommodate lipid more effectively than the abdominal subcutaneous depot [32,35]. The hypertrophic adipocyte of abdominal subcutaneous depot by itself can activate macrophages, produces pro-inflammatory cytokines and insulin resistance [36]. The abdominal subcutaneous adipocyte size has been shown to be positively correlated with cardiovascular risk factors which include plasma glucose, lipid and blood pressure in non-diabetic and diabetic subjects independent of gender, age and body weight [37]. Thiazolidinedione, a peroxisome proliferator activated receptor-γ agonist, reduces insulin resistance and improve metabolic dysfunction by stimulating preadipocytes to differentiate into mature adipocytes [38]. It makes more lipids stored in mature adipocytes and reduces ectopic lipid deposition in other tissues. Therefore, the high capability of subcutaneous adipose tissue to accommodate lipid has a protective effect against lipotoxicity and metabolic disorders [39]. The more in-depth review of this topic can be read elsewhere.
Although several genes has been demonstrated to be involved in body fat distribution in human obesity but their functions remain elusive [27,42-45]. Whether there is a defect of adipocyte-regulated gene expression or function in subcutaneous adipose tissue of non-obese Asian diabetic subjects is unknown.

The study in a large number of non-diabetic Swedish men and women by Andersson et al [27] indicated that abdominal subcutaneous fat cell numbers increased in proportion with increasing abdominal subcutaneous fat mass over the BMI ranges of 18-62 kg/m² but the much larger fat cell size (adipocyte hypertrophy) was significantly increased only in men with BMI <30 kg/m². The increased fat cell size was independently associated with insulin resistance in both men and women but was steeper in men. Alligier et al [46] studied the concurrent changes of abdominal subcutaneous and visceral fat after 56 days of high-fat feeding in 41 non-obese, non-diabetic French men who had no family history of diabetes and observed the large individual variation of the relative distribution of visceral and abdominal subcutaneous fat depots. About 50% of subjects experienced a marked increase of visceral fat deposition whereas others did not. Gene expression analysis from abdominal subcutaneous fat indicated the reduced induction of gene involved in triglyceride synthesis in subcutaneous fat of those men who had visceral fat increased. Anand et al [47] studied adipocyte size from abdominal subcutaneous fat of healthy non-obese South Asian women compared with those of obese Canadian women (BMI ~29 kg/m²). They found that total abdominal subcutaneous fat areas was not different between South Asians and Canadians but adipocyte size of South Asian women was significantly larger and liver fat content was significantly higher despite smaller BMI. The larger adipocyte size was partially accounted for the higher degree of insulin resistance, the lower HDL cholesterol and adiponectin levels observed in non-obese South Asian women. Chandalia et al [48] studied the relationships of body fat distribution and adipocyte size of abdominal subcutaneous depot with insulin resistance in non-obese, non-diabetic South Asian men compared with those of age- and BMI-matched Caucasian men. They found that South Asian men had greater abdominal subcutaneous fat mass, larger adipocyte size and higher insulin resistance (measured by clamp method) than Caucasian men despite similar amount of visceral fat. Adipocyte size was positively correlated with insulin resistance independent of total body fat, abdominal subcutaneous fat or visceral fat mass. In contrast, Meena et al [49] reported omental adipocyte size, although smaller than abdominal subcutaneous adipocyte size, was stronger correlated with HOMA-IR in non-obese, non-diabetic Asian Indian men. However, the relationship was attenuated after adjusting for measures of adiposity. The differences of study design and methods of measurement may explain the discordant results between these studies. Furthermore since body fat distribution particularly of abdominal subcutaneous depot is different among Asian populations [11,50,51], the contribution of the abdominal subcutaneous adipocyte size to systemic insulin resistance in other Asian populations needs to be investigated.

The studies in non-obese diabetic patients or diabetes-prone subjects also support the role of abdominal subcutaneous adipocyte hypertrophy in the generation of insulin resistance. However none of the study was done in Asian diabetic populations. Acosta et al [52] studied abdominal subcutaneous fat of 14 non-obese Caucasian diabetic men and 13 healthy controls and reported significantly larger fat cell volume in diabetic men. The increased fat cell volume was correlated with insulin resistance, lipolysis and TNF-α secretion independent of diabetes status. The expression of gene involving in adipogenesis and adipocyte morphology was inversely correlated with fat cell size in this study. This may indicate the attenuated differentiation capacity of preadipocytes in non-obese diabetic subjects. The studies from a small number of non-obese 1st-degree relatives of Caucasian parents with type 2 diabetes by Hammarsted et al [53] and Henninger et al [54] also showed adipocyte hypertrophy in these diabetes-prone relatives in both men and women compared with age-, sex- and BMI-matched controls who had no history of diabetes in parents. Abdominal subcutaneous adipocyte hypertrophy, independent of waist-hip ratio was associated with insulin resistance and inflammatory markers. However, there was no difference of gene expression of adipogenesis regulator between the groups in this study. These findings indicate that abdominal subcutaneous adipocyte hypertrophy is present long before diabetes develops and contributes to insulin resistance and inflammatory state in non-obese diabetic and non-diabetic subjects independent of total fat mass. The association of adipocyte hypertrophy and insulin resistance is also observed not only in non-obese but also in obese diabetic subjects [55].

These findings support the hypothesis of defective abdominal subcutaneous adipose tissue storage capacity in the development of insulin resistance and its association with excessive visceral or ectopic lipid deposition in non-obese diabetic patients or predisposed-to-diabetes subjects. It is plausible that the defect of abdominal subcutaneous adipose tissue storage capacity could have been observed in non-obese diabetic patients of Asian populations. The study dedicated for this specific population should be performed.
Role of ectopic lipid deposition in non-obese Asian type 2 diabetic patients

Intra-hepatic fat

The prevalence of non-alcoholic fatty liver disease (NAFLD) in non-diabetic subjects who have BMI <25 kg/m² in Asia-Pacific region is ~15–21% [56]. The study in ~2,000 non-diabetic Indian population demonstrated that 75% of subjects with NAFLD had BMI <25 kg/m² and 54% of which had no abdominal obesity [57]. Data from non-obese, East Asian (Chinese, Japanese, Korean) men and women, of which 50–60% had type 2 diabetes indicated similarly high prevalence of fatty liver measured by CT imaging. The prevalence of fatty liver disease in these populations was higher than those of Caucasian or Hispanic populations despite much lower BMI [11,58]. Likewise, the prevalence of NAFLD measured by MRI in non-obese Asian Indians with type 2 diabetes was ~50% whereas it was found in only 2% in BMI-matched non-diabetic controls [13]. There was a strong positive relationship of visceral and intra-hepatic fat content in these non-obese Asians. The high free fatty acid in portal circulation from the increased visceral fat lipolysis increases fatty acid esterification and hepatic fat content [59].

It is well known that the presence of intra-hepatic fat is strongly associated with hepatic insulin resistance and perhaps with muscle insulin resistance in obese, non-diabetic and diabetic subjects [60,61]. Intra-hepatic fat is associated with insulin resistance in both liver and muscle in non-obese, non-diabetic Japanese men [62]. Sharma et al [63] reported higher hepatic gluconeogenesis and insulin resistance in non-obese, non-diabetic Asian Indian men with NAFLD than those of age and BMI-matched men without NAFLD. The studies of the relationships of intra-hepatic fat and insulin resistance in non-obese diabetic patients in Asian population are relatively few. Furukawa et al [64] studied 29 non-obese Japanese diabetic patients and found that 7 had increased liver fat. Patients who had high liver fat had more peripheral insulin resistance than those without although no difference of visceral fat area was observed. The studies in Caucasian populations give similar findings. Hwang et al [65] observed the inverse relationship of intra-hepatic fat content and peripheral insulin sensitivity which was stronger than that of visceral fat in twelve non-obese, non-diabetic Caucasian subjects. Likewise, Gastaldelli et al [66] reported similar amount of intra-hepatic fat content in 24 non-obese Caucasian diabetic patients compared with 19 obese patients despite significantly higher amount of visceral fat in the latter. The inverse correlation with peripheral insulin sensitivity was stronger with the amount of intra-hepatic fat than that of visceral fat. How intra-hepatic fat causes systemic insulin resistance independent of visceral fat is intriguing. Some studies indicated that, after high carbohydrate meal, skeletal muscle insulin resistance can promote hepatic lipogenesis by diverting away glucose from muscle glycogen storage to triacylglycerol synthesis in the liver [67,68]. On the other hand, chronic inflammation of the liver secondary to fat accumulation may increase several inflammatory mediators such as interleukin (IL) and TNF and induces peripheral insulin resistance in the muscle [69]. TNF-α can reduce expression of glucose transporter type 4 (GLUT4) which is important for insulin-dependent glucose uptake at adipocytes and muscle cells [70,71]. It also induces serine phosphorylation of insulin receptor substrate (IRS)-1 and inhibits downstream signaling of phosphatidylinositol-3-kinase [71]. IL-6 induces insulin resistance by impairing the phosphorylation of IRS-1 [70,72]. The presence of these inflammatory mediators has been recently shown to predict the development of insulin resistance and type 2 diabetes in non-obese Finnish men [73]. Intra-hepatic fat, independent of visceral fat, has been shown to be associated with numbers of the cardiometabolic risk in diabetic patients [74].

It should be noted that the evidence of the positive relationships of intra-hepatic fat, insulin resistance and cardiometabolic risk in non-obese Asian populations are largely from non-diabetic subjects, it is speculated that such relationships could be observed in diabetic patients as well.

Intra-myocellular lipid (IMCL)

In human physiology, the over-supply of fatty acids from high fat diet or increased adipose tissue lipolysis is transported into muscle cells by fatty acid transporters, after which it can be oxidized in mitochondria (β-oxidation) or accumulated as intramuscular triacylglycerol in the form of lipid droplets or being metabolized to lipid intermediates [75]. The association of IMCL and muscle insulin resistance has previously been demonstrated in obese, non-diabetic and diabetic subjects as well as lean, non-diabetic offspring of type 2 diabetic subjects. Jacob et al [76], Perseghin et al [77] and Lattuada et al [78] independently reported a significantly increased IMCL content measured by magnetic resonance spectroscopy (MRS) in soleus and tibialis anterior muscles of non-obese, insulin-resistant offspring of type 2 diabetic subjects compared with age- and BMI-matched, insulin sensitive controls. However, only Jacob and Perseghin, not Lattuada demonstrated the strong relationship of IMCL content and insulin resistance. The study of IMCL content and insulin resistance in non-obese Asian diabetic

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patients is rare. Misra et al [79] reported two times higher amount of IMCL in ten non-obese Indian diabetic men compared with sex and BMI-matched healthy control but the relationship of IMCL content and insulin resistance could not be demonstrated. This result in Asian population contradicts those results from Caucasians. It has been known that IMCL can be affected by several factors other than obesity and it is not always associated with insulin resistance. It can be depleted with an acute bout of exercise or can be increased and served as fuel supply in insulin-sensitive endurance exercise training athletes, a phenomenon referred to as “athletes paradox” [80,81]. This may be one of the reasons to explain the inconsistent relationship of IMCL and insulin resistance. Furthermore IMCL can possibly be the result of reduced muscle mitochondrial oxidative capacity of type 2 diabetes although recent evidences prove that this is unlikely to be the case [82–84].

Currently it is believed that the presence of IMCL per se is not the direct cause of muscle insulin resistance. Lipid droplet number and size, the amount of lipid intermediates particularly diacylglycerol and ceramides as well as their subtypes and their cellular location (subsarcolemmal or cytosol) are more important than the amount and may directly involve in muscle insulin resistance of obesity and type 2 diabetes [85]. However, it needs many more studies to understand how they can interfere with skeletal muscle glucose uptake in human physiology. Whether these lipid intermediates or its droplet size and number are altered in non-obese diabetic subjects is unknown. The in-depth review of the role of IMCL and insulin resistance as well as the proposed mechanism of the “athletes paradox” can be read from the references [80,81,86].

**Intra-pancreatic fat**

In contrast with the extensive studies of other regional fat, intra-pancreatic fat has received least attention in the past due to the limitation of investigation particularly with the non-invasive tools. However, with the recent introduction of MRS, the studies of the association of intra-pancreatic fat and metabolic disturbances in healthy and diseased subjects has rapidly emerging [87]. Intra-pancreatic fat measured by MRS includes peri-pancreatic, inter-lobular and intra-lobular adipose tissue and parenchymal fat. Nevertheless, it cannot distinguish the lipid accumulation within acinar and β-cell [88]. Although the presence of intra-pancreatic fat is commonly observed in both obese non-diabetic and diabetic subjects but it is also present in non-obese diabetic subjects [89,90]. By using 6.2% as a cut-off upper limit of pancreatic fat content, the prevalence of intra-pancreatic fat or “Non-alcoholic fatty pancreas disease” (NAFPD) measured by MRS in 1,209 healthy individuals is 33% [91]. The prevalence of NAFPD assessed by trans-abdominal ultrasonography in non-obese, non-diabetic Asian populations was 16–35% [92–94]. The prevalence of NAFPD in non-obese Asian diabetic patients is unknown. It was estimated to be 50% by CT in one study from 98 non-obese Korean diabetic patients [90].

Total intra-pancreatic fat content has been shown to be increased in diabetic compared with BMI-matched, non-diabetic subjects in some but not all studies [88,95–97]. The inconsistency may be explained by the difference of age, tools of measurement and degree of obesity. The recent pathological study in non-obese Japanese subjects indicated no difference of intra-pancreatic fat content between diabetic and non-diabetic subjects [98]. The meta-analysis from a large number of subjects by Singh et al [91] indicated that the presence of intra-pancreatic fat was significantly associated with 2 folds higher risk of diabetes mellitus. Nevertheless the long-term follow-up study contradicts this result. Yamazaki et al [99] followed 813 non-obese, non-diabetic Japanese subjects for 5 years and found no independent association of pancreatic fat (measured by CT attenuation) and incidence of diabetes after adjustment with BMI and intra-hepatic fat content. Since intra-pancreatic fat content is increased with increasing BMI and/or intra-hepatic fat content [96,100] and the latter are strongly associated with diabetes, it is possible that the result of Singh et al study may be falsely positive.

The in-vitro and animal studies indicate that prolonged exposure of human β-cell to free fatty acid or high fat diet respectively can induce β-cell apoptosis and results in β-cell dysfunction [101,102]. It is speculated that the accumulated intra-pancreatic fat may play a role in the development of diabetes in this regard. However, the clinical studies in human gave disappointing results. Total intra-pancreatic fat content is not associated with β-cell function at least in obese glucose intolerance or diabetic subjects in several studies [88,92–96,103]. The morphological study in non-obese subjects by Murakami et al [98] indicated that although fractional β-cell areas was significantly decreased in diabetic compared with age- and BMI-matched non-diabetic subjects but there was no difference of intra-pancreatic fat areas between two groups. Furthermore intra-pancreatic fat was not observed within the islets and its content was not associated with the frequency of β-cell replication, β-cell apoptosis or mean islet size.

The evidence so far demonstrate that intra-pancreatic fat may be an innocent bystander and has no or little influence on β-cell function in human.
Figure 1 Proposed mechanisms of regional adipose tissue in the development of insulin resistance and the increase of cardiovascular risk in non-obese Asian type 2 diabetic patients.

Conclusions

These data indicate that the total body fat content of non-obese Asian type 2 diabetic patients is not different from non-diabetic counterpart but the proportion of visceral fat and intra-hepatic fat is greater. It appears that the increased amount of visceral fat in combination with the increase of liver fat contribute to the development of insulin resistance and the increase of cardiovascular risk in non-obese type 2 diabetes in Asian populations as shown in Fig. 1. The hypertrophic abdominal subcutaneous adipocytes has been shown to contribute to insulin resistance and cardiovascular risk in non-obese, non-diabetic Asian populations as well as in non-obese Caucasian diabetic subjects. This could have been true in non-obese Asian diabetic populations but requires further more study. The role of intra-myocellular lipid and muscle insulin resistance is still uncertain. Intra-pancreatic fat may not be involved in β cell dysfunction in non-obese Asian diabetic population.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed

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