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Double diabetes: A distinct high-risk group?

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Abstract (250 words)

The term double diabetes (DD) has been used to refer to individuals with type 1 diabetes who are overweight, have a family history of type 2 diabetes and/or clinical features of insulin resistance. Several pieces of evidence indicate that individuals who display features of DD are at higher risk of developing future diabetes complications, independent of average glucose control, measured as glycated haemoglobin (HbA1c). Given the increased prevalence of individuals with features of DD, pragmatic criteria are urgently required to identify and stratify this group, which will help with subsequent implementation of more effective personalised interventions.

In this review, we discuss the potential criteria for the clinical identification of individuals with DD, highlighting the strengths and weaknesses of each definition. We also cover potential mechanisms of DD and how these contribute to increased risk of diabetes complications. Special emphasis is placed on the role of estimated glucose disposal rate (eGDR) in the diagnosis of DD, which can be easily incorporated into clinical practice and is predictive of adverse clinical outcome. In addition to the identification of individuals with DD, eGDR has the potential utility to monitor response to different interventions.

Type 1 diabetes is a more heterogeneous condition than initially envisaged and those with features of DD represent a subgroup at higher risk of complications. Pragmatic criteria for the diagnosis of individuals with DD will help with risk stratification, allowing a more personalised and targeted management strategy to improve outcome and quality of life in this population.

Introduction

Type 2 diabetes (T2D), usually due to insulin resistance and gradually progressive pancreatic β-cell failure[1], is a common condition and characterised by high heterogeneity. In contrast, Type 1 diabetes (T1D), insulin deficiency, has been regarded as a condition with a largely uniform phenotype However, the development of insulin resistance in individuals with T1D has led to the emergence of a distinct phenotype of mixed T1D and T2D, or double diabetes. Therefore, classification of diabetes is not that simple and indeed recent work has stratified these individuals into different subgroups. It was suggested that this will help predict disease progression and predisposition to complications, offering the possibility of future individualised and tailored therapies[2,3].

Despite first using the term 'double diabetes' (DD) over a quarter century ago, there is still a lack of clear criteria to define this group of individuals. The earliest description of DD dates back to 1991[4], when Teupe and Bergis demonstrated that T1D individuals who had at least one relative with T2D had worse glycaemic control with increased insulin requirements, and tended to have a higher body weight compared to those without a family history of T2D. The authors, therefore, proposed a subtype of T1D with family history of T2D as having DD. A number of case reports followed describing individuals with DD using similar criteria; the case by Libman and Becker was particularly interesting by demonstrating that features of DD can manifest as early as 5 years of age with full traits of insulin resistance and the metabolic syndrome (MS) evident by the age of 14 years[5]. However, no clear recommendations were made for identifying these individuals or implementing alternative and targeted management strategies.

In this review, we provide an update on DD and attempt to address three main questions:

1) What is the best and most pragmatic measure to identify individuals with DD?
2) Is there a difference in the rate or severity of diabetes complications in DD, and if this is the case, what are the mechanisms involved?
3) To what extent do patients with DD require different management strategies?

Definition of double diabetes

Criteria for the definition of DD to date have relied on the presence of clinical features of insulin resistance, as summarised in two comprehensive review articles (Table 1) [6,7]. While these proposals have raised awareness of the DD population, criteria used to make a diagnosis have been difficult to incorporate into daily clinical practice. In order to provide an accurate definition of DD, we need to explore the strengths and weaknesses of the existing criteria, which can be largely divided into three groups: family history, obesity/MS, and insulin resistance.

1. Family history

There is a genetic predisposition in T1D as concordance rate in monozygotic twins is 5-fold higher than dizygotic twins [8,9]. However, almost 90% of patients report no family history of T1D and therefore the genetic influence is modest. In contrast, the role of genetic factors are far stronger in T2D with 3- and 6-fold increased risk in offspring if one or both parents have type 2 diabetes, respectively [10]. At least 88 genetic loci for T2D have been discovered by linkage and genome-wide association and sequencing (GWAS) studies, where identified loci have been implicated in both pancreatic β-cell function and insulin resistance/MS [11,12]. One particular variant of FTO

)fat mass– and obesity-associated(gene is linked to insulin resistance, increased fat mass and preferential visceral fat distribution, thus increasing T2D risk [13]. Moreover, several common gene variants are also related to insulin resistance in T2D, independently of obesity[14].

In DD, it is possible that individuals with T1D have a genetic predisposition to insulin resistance and T2D, particularly in those with concomitant family history of T2D. Healthy subjects with family history of T2D exhibit a greater degree of insulin resistance and are prone to have higher BMI, and body fat composition, even prior to the development beta-cell failure [15]. A similar mechanism may be operating in double diabetes but not necessarily in the same order; insulin resistance may develop later in the course of T1D, although it can be present at diagnosis and may even contribute to an earlier presentation of T1D. This explains the first description of Teupe and Bergis in 70 T1D patients with a family history of T2D, of a total group of 448 individuals [4]. Those with DD had higher BMI, insulin dose and glycated haemoglobin A1c (HbA1c) compared with the rest of the group. Supported by a larger study of 1,860 T1D individuals aged less than 35 years (from the Finnish Diabetic Nephropathy study), it showed that 620 individuals had a family history of T2D, who again had higher BMI, insulin dose, HbA1c and triglyceride levels.

Data from 1,168 T1D patients from the Diabetes Control and Complication study (DCCT) has shown that a family history of T2D was related to greater central weight gain, insulin dose and triglyceride levels in the intensive arm of the study [16]. Moreover, family history of T2D was also related to elevated LDL cholesterol and apolipoprotein B levels in both study arms. The greater weight gain in the intensive arm suggests that intensive insulin therapy to optimise glycaemia further increases the risk of developing DD in susceptible individuals.

Despite the increase in vascular risk factors in T1D with a family history of T2D, the association with diabetes complications is not always clear. A cross-sectional study of 3,162 T1D individuals, aged 15-60 years from the EURODIAB IDDM Complications Study, only showed an association between a family history of T2D and albuminuria in female subjects [17]. Similarly, an observational study in 658 T1D patients failed to demonstrate causal relationship between a family history of T2D and coronary artery disease after adjustment for confounders [18]. However, it can be disputed that the number of individuals studied is limited and the period of follow up is relatively short to make concrete conclusions.

Taken together, a family history of T2D is a risk for developing poorer metabolic traits and obesity in T1D, yet it does not appear to be a strong independent predictor of diabetes-related complications. However, studies have been conducted on relatively small numbers of younger individuals and silent vascular events were not ruled out, which have been shown to affect up to a fifth of asymptomatic T2D individuals [19], and this may explain the negative findings. Further adequately powered longer-term studies are required to understand the role of a family history of T2D in predisposing to complications in individuals with T1D.

2. Excessive weight gain/obesity and metabolic syndrome (MS)

Insulin is an anabolic hormone, so intensification of therapy is likely to lead to weight gain. While this is an acceptable compromise in those with poor glycaemic control, continued administration of insulin subcutaneously can lead to peripheral resistance to the action of this hormone[20,21], consequently increasing DD risk. The secondary analysis of the whole DCCT study population showed that T1D individuals whose weight gain stratified into the fourth quartile (excessive gainers) had higher insulin dose, blood pressure and non-HDL cholesterol [22]. Moreover, individuals whose BMI increased over 4.39 kg/m^2 during DCCT study period, had greater intima-media thickness and displayed a trend toward greater coronary artery calcium scores [23], providing strong evidence for vascular pathology in this group. Also, excessive gainers displayed tendency towards higher CV events after a mean follow-up of 26 years [24].

We should, nevertheless, be careful when interpreting weight data, as initial moderate weight gain following diagnosis of T1D correlates with improved HbA1c and reduction in mortality. However, excessive weight gain, reaching a BMI $\geq$30 kg/m^2, has repeatedly shown an association with increased mortality [25,26].

Therefore, while weight gain should not be used as the sole identifier for DD, excessive weight gain, particularly in those with BMI ≥30 kg/m^2, may provide a simple clinical marker to identify DD and risk of future adverse vascular outcome.

The presence of MS has been proposed as a more comprehensive marker for the identification of DD. MS integrates central obesity and other traditional CV risk factors including hypertension, hypertriglyceridaemia and decreased levels of high density lipoprotein (HDL) cholesterol. The EURODIAB Prospective Complications Study)PCS(, observed 3,250 T1D patients for 7 years from 16 European countries and documented that some components of the MS were associated with increased CV and all-cause mortality [27].

The relationship between MS and diabetes-related complications among adults with T1D has been extensively reviewed by Gingras et al. [28], and the authors concluded that the presence of MS is associated with increased risk of both micro- and macrovascular disease.

The association of MS with future complications can depend on the type of definition used for MS with some studies, albeit not all, suggesting that WHO definition of MS is the best predictor of future complications [29,30]. However, it is not practical in daily clinical practice to use a binary variable like MS to assess the risk of future complications, particularly in the presence of various definitions. Also, the effects of managing components of MS will not be apparent until an individual drops into the non-MS range, which may be a challenge in some, making patients frustrated and potentially disengaged. Therefore, MS has too many flaws to be a reliable and practical marker of DD.

3. Insulin resistance and estimated glucose disposal rate (eGDR)

Insulin resistance is associated with asymptomatic atherosclerosis and coronary artery disease in individuals without diabetes [31,32]. A meta-analysis of 65 studies, which included 516,325 adults without diabetes, has shown that insulin resistance, measured by HOMA-IR, is a good predictor of CV disease [33]. In line with these findings, insulin resistance in T1D has been associated with increased risk of cardiovascular disease [34]. Furthermore, the CACTI study demonstrated that insulin resistance, measured by clamp techniques, predicted the presence of coronary artery calcification in T1D [35].

The gold standard method to measure insulin resistance is the euglycaemic-hyperinsulinemic clamp [36]. However, due to the invasive and time-consuming nature of the procedure, it is not suitable for daily clinical practice. Estimated glucose disposal rate (eGDR) has been proposed as an alternative method to measure insulin resistance that is easy to apply in clinical settings. The eGDR score was originally developed and validated by the euglycaemic-hyperinsulinemic clamp in a subset of 24 T1D patients from the Pittsburgh EDC study [37]. William and colleagues initially calculated eGDR using clinical factors including waist-hip ratio (WHR), presence of hypertension and HbA1c. However, the authors also stated that replacing WHR with either BMI or waist circumferences (WC) provided a comparable association with insulin resistance [37-39]. All formulae for eGDR calculation are displayed in Box 1.

Box 1. Formulae for eGDR calculation

$$eGDR_{WHR} = 24.31 – (12.22 \text{ x } WHR(– (3.29 \text{ x } HTN(– (0.57 \text{ x } HbA1c($$

$$eGDR_{WC} = 21.16 – (0.09 \text{ x } WC) – (3.41 \text{ x } HTN) – (0.55 \text{ x } HbA1c)$$

$$eGDR_{BMI} = 19.02 – (0.22 \text{ x } BMI) – (3.26 \text{ x } HTN) – (0.61 \text{ x } HbA1c)$$

WHR = waist-hip ratio
WC = waist circumference, cm
BMI = body-mass index, kg/m^2
HTN = hypertension, 1=yes, 0=no
HbA1c = glycated haemoglobin A1c, %

Similar to MS, eGDR incorporates weight and blood pressure, however, it is a continuous variable allowing to monitor the effectiveness of a particular therapy, making it attractive for clinical use. This is particularly important as a decrease in eGDR is associated with increased risk of nephropathy [40], peripheral vascular disease [41], coronary artery disease [42,43] and death [43] with lower values conferring greater risk. The result from DCCT study also supports the relationship between low eGDR and increased risk of both micro- and macrovascular complications [44], and shows superiority at predicting complications compared with the use of MS to define DD.

While eGDR appears to be a promising marker to identify DD, the cut off value requires careful consideration. Nyström et al. performed a nationwide cohort study on 17,050 T1D individuals, using data from healthcare registers in Sweden. Patients were categorized into 4 eGDR groups: <4, 4 to 5.99, 6 to 7.99, and ≤8. Clinical outcomes, including CV events and death, were collected using national registry data, over a median follow-up of 7.1 years. An eGDR <8 was associated with increased CV risk or death compared to those with eGDR $\geq$8. The risk further increased with lower eGDR values (Fig. 1) [39]. Interestingly, survival rate of individuals with eGDR $\geq$8 was identical to a matched reference population. Hence, the eGDR value of <8 is convincingly suitable to identify those with DD among individuals with T1D, with higher risk incurred in those with progressively lower eGDR.

Prevalence of double diabetes according to each definition

Using obesity (BMI$\geq$30 kg/m^2) as a measurement, the prevalence of DD amongst T1D can reach 30%, particularly as the prevalence of obesity has been increasing in the T1D population (Fig. 2) [45]. The prevalence of obesity in the DCCT/EDIC study has shown an increase from 2% at baseline (1983-1989) to 28% at 12 years of follow-up [46]. This may be an easy marker to use but it is likely to miss significant number of individuals with DD and therefore more accurate measures are needed.

When MS is applied for identification of DD, the prevalence is dependent on study period, population analysed, and MS definition used (Fig. 3). A range of 30-45% of T1D individuals have MS and therefore up to half the patients will have DD using this criterion. However, given the binary nature of MS definition, its only possible role in clinical management is identification of individuals at risk and it is not a useful marker to assess response to a particular management strategy.

In the study by Nyström et al [39], the prevalence of DD in T1D at the beginning of the study was 51%, when applying eGDR<8 as a proposed diagnostic criterion. The increased risk of complications with lower eGDR, makes this a suitable marker to assess response to a particular intervention, in contrast to MS.

The increasing trend of DD is consistent across all measurements. Therefore, unless acted upon, DD will possibly become the predominant phenotype in T1D in next few decades.

Pathogenesis of double diabetes

If we accept that T1D individuals who are overweight are likely to form the core group of DD, then the pathogenic mechanisms are related to genetic predisposition and environmental factors. The latter factors can interact with T1D duration making DD a time-dependent condition. Even those with initial good insulin sensitivity and no genetic predisposition may transition to DD secondary to unhealthy lifestyle that leads to weight gain [47]. While genetic predisposition is non-modifiable, environmental factors can be controlled thus limiting the prevalence of DD. Exposure to obesogenic environments affect the rates of overweight and obesity, particularly among children. Almost 32% and 16% of children with poor physical activity and unhealthy nutritional environment are overweight and obese, whereby 24% and 8% of those living in healthier environments are overweight and obese, respectively [48]. However, the percentage of younger T1D individuals with a weight problem is higher than those without diabetes [49,50], indicating the presence of additional mechanisms. For example, repeated hypoglycaemia or even the fear of hypoglycaemia results in maladaptive eating habits that favour the development of obesity [51]. Peripheral insulin resistance precipitated by subcutaneous insulin administration rather than the physiological portal vein delivery, is another additional factor for the development of DD [21,34].

Therefore, DD in T1D develops secondary to a combination of lifestyle behaviour, akin to individuals without diabetes, and, diabetes-specific mechanisms related to hypoglycaemia and the non-physiological administration of insulin subcutaneously.

Double diabetes, glycaemic control and complications

The DCCT and the extended observational EDIC studies have clearly shown that improving glycaemia, measured as a reduction in HbA1c, decreases microvascular complications and long term macrovascular disease [52,53]. However, it became apparent that there was a great heterogeneity in the rate of complications, indicating that factors other than HbA1c also had a role.

Merger and colleagues conducted a cross-sectional study to measure the prevalence of comorbidities in DD by analysing data in the DPV]Diabetes-Patienten Verlaufsdokumentation[registry from 392 specialized centres in Germany and Austria [54]. DD was defined as individuals with T1D and MS using the Third National Cholesterol Education Program Adult Treatment Panel (NCEP/ATPIII) criteria. Of a total of 31,119 T1D individuals, 7,926 had DD (25.5%), a group that displayed markedly higher micro- and macrovascular complications, even after adjustments for age, sex and diabetes duration. In a subgroup analysis of individuals with well-controlled glycaemia (HbA1c <7% or 53mmol/mol), 1892 of 9203 had DD (20.6%), and showed reduced risk of complications compared to those with inadequate glucose control. However, this group still had up to 3.5 times higher rate of complications compared with T1D patients without MS having identical HbA1c. More worryingly, the rate of complications in the well-controlled DD subgroup was higher than all T1D without MS regardless of glycaemic control (Fig. 4).

In addition to increased rate of complications, mortality is also increased in individuals with DD. The hazard ratio (HR) for diabetes-related mortality from FinnDiane study was significantly higher in DD (defined as presence of MS by WHO criteria), compared to T1D without MS (adjusted HR 2.52 [95%CI: 1.53-4.16]) [29]. All-cause mortality in DD defined by eGDR<8 was increased 1.6-fold compared to those with eGDR $\geq$8 [39].

Potential mechanisms for increased complications in double diabetes

A key component of DD that may increase complication rate is insulin resistance and the need for relatively larger dose of subcutaneous insulin. While HbA1c on its own does not explain the increased rate of complications in DD, other glycaemic markers such as glucose variability (GV) and/or hypoglycaemia may have a role. Alterations in traditional CV risk factors such as dyslipidaemia and hypertension are likely to play a role in increased rate of complications. The potential mechanisms for increased complications in DD are illustrated in Fig. 5.

The role of glycaemia

The observational study by Merger and colleagues [54] suggests that individuals with DD who are generally more obese than those with T1D, tend to have higher HbA1c, which may, at least in part, be responsible for the increased risk of complications in DD. It should be noted that HbA1c measures average glucose levels and does not address GV or hypoglycaemia, both of which appear to be associated with adverse vascular outcome [55,56]. In particular, higher insulin doses, commonly used in DD, may lead to increased risk of hypoglycaemia [57], which in turn enhances the inflammatory/thrombotic milieu thus contributing to vascular pathology [58]. Moreover, the potential for larger fluctuations in glucose levels in this population may implicate GV in the increased risk of complications. However, these are merely hypotheses at present and studies are required to establish whether individuals with DD experience more hypoglycaemic events and/or higher GV, particularly in those with well controlled HbA1c. If a difference is detected, longitudinal studies are warranted to understand the relationship between these glycaemic markers and vascular complications in DD.

The role of Insulin resistance

Insulin resistance is associated with an enhanced inflammatory environment due to the release of cytokines by adipose tissue macrophages [59] or inflammatory proteins such as complement by adipocytes [60]. This in turn enhances insulin resistance by interfering with insulin-mediated phosphinositide-3 kinase (PI3K) pathway [61,62], creating a vicious cycle. Interestingly, blocking inflammatory cytokines with the use of interleukin-1 antagonist can improve insulin sensitivity in insulin resistant patients with

T1D [63]. Moreover, systemic cytokines leakage into the circulation contributes to low grade generalized inflammatory milieu, which in turn promotes endothelial dysfunction, the earliest abnormality in the atherosclerotic process [64].

Insulin resistance also increases lipolysis leading to non-esterified free fatty acid flux into the systemic circulation, where triglyceride deposition in muscle and liver tissues augments insulin resistance [65]. Insulin resistance also leads to hyperglycaemia through unsuppressed hepatic gluconeogenesis and decreased muscular glucose uptake [66,67], thus resulting in higher insulin requirements. Insulin resistance contributes to an increase in blood pressure by diminishing the vasodilatation efficiency and promoting smooth muscle growth. Moreover, insulin resistance impairs PI3K-dependent signalling pathway while keeping the mitogen-activated protein kinase (MAPK)-dependent pathway intact [68], resulting in imbalance between the two pathways. Compensatory hyperinsulinemia, therefore, increases production of the vasoconstrictor endothelin-1 [69], which opposes vasodilator action of nitric oxide [70], through the overstimulation of the unaffected MAPK pathway [71]. The overstimulation of MAPK pathway additionally activates vascular smooth muscle cell migration and proliferation [72], leading to vascular wall thickening and increased peripheral vascular resistance.

Apart from insulin-signalling pathways, hyperinsulinemia results in sodium retention [73-75] through a direct anti-natriuretic effect and by upregulation of the renin-angiotensin-aldosterone system [76].

Other than the inflammatory environment, insulin resistance predisposes to hypofibrinolysis leading to a thrombotic environment through altered levels and/or activity of coagulation factors such as fibrinogen [77,78], plasminogen activator inhibitor-1 [79,80] and the inflammatory thrombotic protein complement C3 [81,82].

Conclusions and future directions

Evidence to date indicates that individuals with features of DD have increased risk of complications yet the clinical management of this group remains similar to others with T1D. A difficulty is the absence of reliable criteria to identify individuals with DD. Relying on a family history of T2D is inadequate while the presence of the MS is problematic given the different definitions and the difficulty in incorporating into routine clinical practice. This leaves eGDR as a credible measure of DD, which is easy to adapt clinically and has the advantage of offering a numerical value that can be used to monitor response to a particular intervention, similarly to HbA1c.

We need to better understand the mechanisms leading to DD and the pathways implicated in increased risk of complications in this group. This includes the effects of different glycaemic markers such as hypoglycaemia and GV, made possible with modern glucose monitoring strategies that rely on continuous glucose values rather than sporadic capillary glucose measurements. The contribution of genetic and environmental factors to the development of DD requires further research, including the role of different insulin preparations and mode of administration. For example, it is not entirely clear whether insulin pump-treated patients have different rates of DD compared with those on multiple daily injection.

The most challenging aspect, however, is clarifying the best treatment strategy in individuals with DD, a group in itself with varying degree of risk. It is possible that routine use of eGDR will allow risk stratification, potentially using this marker as an adjunct to HbA1c when assessing individuals with T1D. Naturally, lifestyle changes should be advocated in individuals with DD, including healthy diet and regular exercise. However, more sophisticated diets may be required for effective weight loss and possibly adjunctive therapy with agents that promote an increase in eGDR. Work is also needed to elucidate whether more aggressive vascular protective strategies are required, and at an early age, in the form of blood pressure lowering anti-hyperlipidaemic and anti-thrombotic agents, which will help to reduce morbidity and improve quality of life in these patients.

List of Abbreviations

CV	cardiovascular
DCCT	the Diabetes Control and Complication study
DD	double diabetes
EDIC	the Epidemiology of Diabetes Interventions and Complications study
eGDR	estimated glucose disposal rate
FinnDiane	the Finnish Diabetic Nephropathy study
GV	glucose variability
MAPK	Mitogen-activated protein kinase
MS	metabolic syndrome
PAI-1	plasminogen activator inhibitor-1
PI3K	insulin-mediated phosphinositide-3 kinase
T1D	type 1 diabetes
T2D	type 2 diabetes
WC	waist circumferences
WHR	waist-hip ratio

Conflicts of interest

All authors have no conflict of interest to be declared.

Author contributions

NK was responsible for drafting and writing of the manuscript, searching of literature and interpreting of data. RAA was responsible for the drafting and writing of the manuscript and critical revision of important intellectual content. SP, MC, and RASA were responsible for critical revision of important intellectual content. All authors approved the version to be published

Figure legends

Fig. 1. Estimated glucose disposal rate (eGDR) and mortality in type 1 diabetes (T1D). All-cause mortality was related to eGDR, calculated using waist circumference, in 17,050 individuals with T1D diabetes. Data were adapted from [39].

Fig. 2. Temporal patterns of overweight and obesity in type 1 diabetes. Data were modified from [45].

Fig. 3. Prevalence of metabolic syndrome (MS) in type 1 diabetes. The role of different MS definitions in predicting double diabetes is shown. of the MS are reviewed. Data were obtained from references [29,30,39,43,44,83-86].

Fig. 4. Prevalence of diabetes complications in individuals with type 1 diabetes (T1D) and metabolic syndrome (MS). Complication rates (a, b) and risk ratios (c, d) of diabetes complications is shown in the presence and absence of MS in individuals withT1D. (CHD, coronary heart disease; MI, myocardial infarction; PAD, peripheral arterial disease; DR, diabetic retinopathy; PDR, proliferative retinopathy; ALB, albuminuria). Data were modified from [54].

Fig. 5 Overview of the mechanisms for increased risk of complications in double diabetes. Insulin resistance and obesity create a low-grade inflammatory milieu which aggravates insulin resistance. This, in turn, leads to hyperglycemia by decreasing glucose uptake in peripheral tissue and increasing hepatic gluconeogenesis. Insulin resistance also causes atherogenic low-density lipoprotein (LDL) cholesterol oxidation and hypertension by various mechanisms. Hyperglycaemia, atherogenic dyslipidaemia and hypertension promote endothelial dysfunction and atherosclerotic plaque formation. Insulin resistance and inflammation sequentially promote hypofibrinolysis leading to prothrombotic clot formation and vascular occlusion (IL-6, interleukin 6; TNF-α, tumor necrosis factor α; PAI-1, plasminogen activator inhibitor 1; C3, complement C3; FFA, free fatty acid; sdLDL, small-dense LDL; oxLDL, oxidized LDL; NO, nitric oxide; ET-1, endothelin-1; PKC, protein kinase pathway C; AGEs, advanced glycation end products; MAPK, mitogen-activated protein kinase).

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