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Review

Insulin resistance is a cardiovascular risk factor in humans

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ABSTRACT

Diabetes is a common metabolic disorder associated to elevated cardiovascular morbidity and mortality that is not explained by hyperglycemia or traditional cardiovascular risk factors such as smoking or hypercholesterolemia. Intensive glycemic control with insulin that achieves near-normal glycemia does not reduce significantly macrovascular complications compared with conventional glycemic control. Cardiovascular disease continues to develop in patients with diabetes despite adequate glycemic control. In contrast, intensive control with metformin (leading to insulin resistance improvement) reduces diabetes complications, including cardiovascular events, suggesting that enhancement of insulin sensitivity rather than plasma glucose level has a major role improving diabetes outcomes. Accordingly, insulin resistance estimated by glucose tolerance tests is better predictor of future cardiovascular events than fasting glucose level in nondiabetic individuals. Insulin resistance precedes for decades the clinical onset of type 2 diabetes and deteriorates metabolic control of type 1 diabetes. Numerous investigations including cross-sectional and prospective studies, meta-analyses, and systematic reviews provide compelling evidence that insulin resistance by itself is a cardiovascular risk factor in a variety of population groups, including the general population and patients with diabetes. Several estimations of insulin resistance have been consistently associated with elevated rate of cardiovascular events independently of other cardiovascular risk factors and diabetes status. The clinical expression of insulin resistance (the metabolic syndrome or any of its components including obesity, hyperinsulinemia, hypertension, and dyslipemia) has been related to cardiovascular disease as well. An estimation conducted by the Archimedes model confirms that insulin resistance is the most important single cause of coronary artery disease.

1. Introduction

In 1922, Levine el al. observed that an altered carbohydrate metabolism was a major factor in the etiology of ischemic heart disease. Since then, diabetes has been consistently associated with elevated cardiovascular morbidity and mortality that is not explained by hyperglycemia or traditional risk factors such as smoking or hypercholesterolemia [1–3]. Normoglycemic subjects who subsequently develop type 2 diabetes (T2D) experience increased cardiovascular risk for years before the clinical onset of diabetes [4]. Further, the best accomplished glycemic control that jeopardizes quality of life and survival does not prevent macrovascular complications of diabetes from occurring. Patients with diabetes continue to endure widespread vascular damage regardless intensive glycemic control. Accordingly, blood levels of either glycosylated hemoglobin or fasting glucose do not predict the incidence of cardiovascular events associated with diabetes in prospective studies [5,6]. Insulin resistance occurs for decades before the diagnosis of T2D and worsens the insulin-deficient state of type 1 diabetes (T1D). Patients with diabetes and severe insulin resistance require larger doses of insulin to achieve metabolic control compared to those who are more-insulin sensitive. Insulin resistance by itself is a major cardiovascular risk factor in healthy

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation; BMI, body mass index; DCCT, Diabetes Control and Complications Trial; DECODE, Diabetes Epidemiology Collaborative Analysis of Diagnosis Criteria in Europe; EDIC, Diabetes Interventions and Complications; HOMA-IR, homeostasis model assessment-insulin resistance; NHANES, National health and Nutrition Examination Survey; T1D, type 1 diabetes; T2D, type 2 diabetes; UGDP, University Group of Diabetes Program; UKPDS, United Kingdom Prospective Diabetes Study.

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persons and patients with diabetes, although the pathogenic mechanisms underlying the vascular injury linked to insulin resistance remain undefined.

1.1. Insulin resistance is independently associated with elevated cardiovascular risk in nondiabetic individuals

Insulin resistance is the most important single cause of coronary artery disease in an estimation conducted by the Archimedes model. The model calculated the proportion of myocardial infarctions that would be prevented by maintaining insulin resistance and other cardiovascular risk factors at healthy levels. Data from the National Health and Nutrition Examination Survey (NHANES) 1998–2004 were used to create a simulated population representative of young adults in the US. This population was then entered into a series of simulated clinical trials. Each trial had a control arm (all risk factors were allowed to progress without interventions) and a treatment arm (a risk factor was held to its value in young healthy adults). The trials continued for 60 years. Approximately 50% of young adults will experience some degree of insulin resistance. The risk of coronary artery disease is nearly three times greater in those who develop insulin resistance than in those who do not develop insulin resistance. Normalizing insulin resistance reduced cardiovascular risk by approximately 55% in subjects with insulin resistance. Insulin resistance was the most important single risk factor for coronary artery disease in young adults, being responsible for approximately 42% of myocardial infarctions. The next most important determinant of coronary artery disease is systolic hypertension, prevention of which would reduce myocardial infarctions by approximately 36%. Following systolic blood pressure, the most important causes of coronary artery disease are HDL-c (31%), body mass index (BMI) (21%), LDL-c (16%), triglycerides (10%), fasting plasma glucose and smoking (both approximately 9%) and family history (4%) [7].

Numerous cross-sectional and prospective studies provide clinical evidence that insulin resistance is a major cardiovascular risk factor in nondiabetic subjects, independently of other risk factors.

1.1.1. Investigations that assess insulin resistance by parameters derived from oral glucose tolerance tests in nondiabetic subjects

Soon after the recognition that glucose intolerance was commonly present in patients with coronary heart disease, a number of cross-sectional and case-control studies investigated the association of insulin resistance with cardiovascular diseases in nondiabetic subjects. These earlier investigations estimated tissue sensitivity to insulin predominantly by plasma glucose and insulin levels during an oral glucose tolerance test. Their results consistently showed that insulin resistance in nondiabetic subjects is associated with cardiovascular disease. Normoglycemic patients with coronary artery disease, premature coronary heart disease, peripheral vascular disease, and ischemic cerebrovascular disease show higher prevalence of impaired glucose tolerance compared to control subjects. In nondiabetic patients with peripheral vascular disease, insulin resistance was much more frequently seen than fasting hypercholesterolemia, suggesting that an altered glucose metabolism is an important causative factor of vascular injury. Population-based investigations also find a cross-sectional association between insulin resistance and macrovascular disease in nondiabetic individuals [5].

Several prospective studies show that impaired glucose tolerance at baseline is an independent predictor of incident cardiovascular disease among nondiabetic population groups, including the Busselton study [8], the Helsinki Policemen Study [9], the Whitehall study [10], the Chicago People Gas Company study [11], and the Study of Men Born in 1913 [12].

Impaired glucose tolerance is a better independent predictor of cardiovascular disease and all-cause mortality than fasting glycemia in nondiabetic individuals. The Diabetes Epidemiology Collaborative Analysis of Diagnosis Criteria in Europe (DECODE) is a cluster of prospective European studies that possesses a large database and a long follow-up. Analyses of the DECODE database show that elevated glycemia 2-h after glucose load is a better independent predictor of cardiovascular and all-cause mortality than fasting glycemia. Plasma glucose 2-h after glucose load enables detection of individuals with insulin resistance who are at the greatest risk of cardiovascular death while fasting glycemia alone does not identify such high-risk subjects [13,14].

In a systematic review and meta-analysis of cohort studies, there was an association between 2-h glucose level after glucose load (insulin resistance) and increased risk of cardiovascular events independently of other risk factors in nondiabetic subjects [15].

A meta-analysis conducted to summarize the quantitative association of fasting glycemia and post-challenge glucose level with cardiovascular risk from prospective studies shows that the association of post-load glycemia with cardiovascular risk is stronger than that of fasting glycemia [16].

In a quantitative review of prospective studies, impaired glucose tolerance and impaired fasting glucose were associated with modest increases in the risk for cardiovascular disease, independently of conventional cardiovascular risk factors [17]. Similar results were found in the Reykjavik study, a population-based study [18].

1.1.2. Investigations that assess insulin resistance by the homeostasis model assessment of insulin resistance (HOMA-IR) in nondiabetic subjects

The prevalence of cardiovascular disease is more than 6-fold higher in the Framingham (US) population than in Fukuoka (Japan) subjects. Standard cardiovascular risk factors do not account for the large difference in the prevalence of cardiovascular disease between the two population groups. Fukuoka subjects show enhanced insulin sensitivity (HOMA-IR), lower BMI, and higher HDL-c levels compared to their Framingham counterparts. The different degree of insulin resistance may contribute to explain the remarkable difference of cardiovascular risk between the two population groups [3].

Multiple prospective studies reveal an association of insulin resistance estimated by the HOMA-IR and incidence of cardiovascular disease in nondiabetic persons.

The San Antonio Heart Study is a population-based prospective trial that showed that insulin resistance (HOMA-IR) is responsible for the increased cardiovascular risk that characterizes the prediabetic state. Subjects with higher HOMA-IR values at baseline show increased cardiovascular risk compared to those with lower HOMA-IR. Insulin resistance is present for many years before the diagnosis of diabetes and causes subclinical vascular injury. Normoglycemic individuals with insulin resistance are already at increased risk of cardiovascular disease years before the onset of clinical diabetes [19,20].

The Veterans Affairs High Density Lipoprotein Intervention Trial examined the effect of insulin resistance on the incidence of major cardiovascular events in men with known coronary heart disease (and therefore, high cardiovascular risk). Patients with insulin resistance (both with diabetes and without diabetes) had a higher relative risk of a cardiovascular event compared with individuals without insulin resistance. In men with known coronary heart disease, baseline insulin resistance (regardless of the diabetes state) is associated with higher risk of incident cardiovascular events [21].

The impact of insulin resistance (HOMA-IR index) on the

incidence of vascular events was investigated over 2.3 years in a prospective cohort study that recruited patients undergoing coronary angiography with (21%) and without T2D. Insulin resistance at baseline predicted vascular events after controlling for risk factors in Cox regression analysis. Additional adjustment for the presence of T2D revealed that HOMA-IR also predicts vascular events independently from diabetes status, suggesting that insulin resistance by itself is a cardiovascular risk factor [22].

Three population-based prospective studies in diverse population groups consistently find that higher HOMA-IR values at baseline are associated with increased incidence of cardiovascular events at follow-up, after adjustment for confounders. Insulin resistance is an independent predictor of cardiovascular disease [23–25].

A prospective study compared the predictive value of two measures of insulin resistance, the HOMA-IR and the ISI(1,120) on the incidence of cardiovascular disease in nondiabetic subjects over 7-year of follow-up. Both estimations of insulin resistance were related to incident cardiovascular disease, but ISI(1,120) levels predicted better than the HOMA-IR the incidence of cardiovascular disease in multivariate analyses [26].

A systematic review and two meta-analyses confirm that insulin resistance as measured by HOMA-IR is independently associated with greater risk of incident cardiovascular disease and all-cause mortality in nondiabetic adults [27,28]. Further, the HOMA-IR index is a better predictor of incident cardiovascular events than fasting glucose or insulin levels in nondiabetic adults [27].

Prospective studies conducted in patients with coronary artery disease show that insulin resistance evaluated at study entry by HOMA-IR is independently associated with new cardiovascular events and mortality during the follow-up. More insulin-resistant patients at baseline have increased cardiovascular risk at follow-up [29,30].

1.1.3. Investigations that measure insulin-mediated whole-body glucose disposal (M value) to assess insulin resistance in nondiabetic individuals

Prospective studies show that insulin resistance (evaluated by insulin-mediated whole-body glucose disposal) predicts the development of cardiovascular disease independently of other risk factors in nondiabetic participants. The presence of insulin resistance identifies a subset of the healthy nonobese population who will develop cardiovascular disease, suggesting that insulin resistance makes a major contribution to cardiovascular disease [31,32].

A cross-sectional study of middle-aged individuals without diabetes investigated the association of fasting glycemia, 2-h glycemia after glucose load and insulin resistance (assessed by the hyperinsulinemic euglycemic clamp) with cardiovascular risk estimated using the Framingham risk score. Insulin resistance was associated with elevated cardiovascular risk after adjusting for fasting glycemia, suggesting that insulin resistance is the primary factor responsible for the increased cardiovascular risk associated to impaired glucose metabolism [33].

2. Investigations that assess insulin resistance by its clinical expression

The clinical expression of insulin resistance is the metabolic syndrome or its individual components, such as hyperinsulinemia, dyslipemia (hypertriglyceridemia and low HDL-c), systolic hypertension, and obesity.

Fasting hyperinsulinemia in nondiabetic subjects has been independently associated with cardiovascular disease in cross-sectional and prospective studies, such as San Antonio Heart Study [4,34] and a nested case-control of the Quebec Cardiovascular Study [35].

Fasting hyperinsulinemia is also associated with an increased risk of new cardiovascular events in nondiabetic men with coronary heart disease in prospective studies [36].

Dyslipemia associated with insulin resistance (hypertryglyceridemia and low HDL-c) is consistently related with increased risk of cardiovascular disease in cross-sectional and prospective analyses. In a cross-sectional study of the Third National Health and Nutrition Examination Survey (NHANES III), low plasma HDL-c level is an independent predictor of prevalent coronary heart disease [37]. Prospective studies have shown an independent association of hypertriglyceridemia and incident cardiovascular disease in the general population and patients with impaired glucose tolerance [12,38,39].

The metabolic syndrome has been independently associated with cardiovascular disease in cross-sectional and prospective investigations among nondiabetic subjects [22,40–44].

A meta-analysis of longitudinal studies confirms that subjects with the metabolic syndrome are at increased risk of cardiovascular events and death independently of traditional risk factors compared to those without the metabolic syndrome [45].

2.1. Insulin resistance is independently associated with cardiovascular risk in patients with type 1 diabetes

2.1.1. Glycemic control and cardiovascular disease in patients with type 1 diabetes

Evidence that intensive versus standard glycemic control offers a substantial clinical benefit regarding macrovascular complications or all-cause mortality in patients with T1D is inconclusive. Accordingly, prospective studies show that the strength of glycemic control parameters (fasting glycemia or glycosylated hemoglobin level) to predict macrovascular injury is unsatisfactory [6,46–49].

The Diabetes Control and Complications Trial (DCCT) is a prospective study that examined whether intensive insulin therapy with the goal of maintaining glycemia close to the normal range could decrease vascular complications in patients with T1D compared to standard therapy. There was no significant effect of treatment (intensive or conventional) on cardiovascular disease or all-cause mortality (there were seven deaths in the intensive-treatment group and four in the conventional-treatment group). There was no reduction in cardiovascular events or mortality with intensive glycemic control compared with standard care [50]. At the close of DCCT in 1993, most patients accepted to participate in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, a long-term observational study of the original DCCT cohort. Progression of carotid intima-media thickness from years 1–12 between DCCT intensive and conventional treatment groups was not different after adjusting for confounders [51,52]. In 2005, the incidence of cardiovascular disease in participants of the DCCT-EDIC study remained low, precluding multivariate analyses and definitive assessment of treatment effects on the risk of the different types of cardiovascular events [53]. The degree of coronary calcification was measured with computed tomography in EDIC patients at 8 years after the end of the DCCT. There was no substantial influence of the prior conventional or intensive treatment during the DCCT on the prevalence of coronary artery calcification [54]. Heart function was evaluated in EDIC patients to assess the influence of intensive versus conventional therapy during the DCCT on cardiac parameters. There was no treatment effect on end-diastolic volume, end-systolic volume, stroke volume, cardiac output, left ventricle mass, ejection fraction, left ventricle mass/end diastolic volume ratio, or aortic elasticity [55].

A systematic literature review of randomized controlled trials aimed to assess the effects of intensive versus conventional

glycemic control in patients with T1D concluded that macrovascular outcomes (stroke and myocardial infarction) occurred rarely and no firm evidence could be established regarding these outcomes [56].

Major adverse effects of intensive glycemic control include severe hypoglycemia and weight gain. Weight gain associated to intensive insulin therapy magnifies insulin resistance and may increase cardiovascular risk [57,58]. Obesity (BMI $\geq$ 30) at year 6 of the DCCT-EDIC has been associated with greater carotid intima-media thickness progression from years 6–12 [52]. The prevalence of overweight and obesity in children with T1D is 38.5%. A higher prevalence of the metabolic syndrome and hypertension has been documented in the overweight/obese children with T1D compared with normal-weight children [59].

2.1.2. Insulin resistance is associated with cardiovascular disease in patients with type 1 diabetes

Numerous investigations link insulin resistance by itself with cardiovascular disease in patients with T1D.

In 1968, Martin et al. reported an association between insulin resistance and prevalent macrovascular disease in a cross-sectional study, suggesting that insulin resistance is a cardiovascular risk factor in patients with T1D. There was no relation between the fasting glycemia and the vascular state [46]. A prospective study with the same participants confirmed the association of insulin resistance to poor vascular prognosis in patients with T1D. Baseline insulin resistance was associated with progression of atherosclerosis and death from vascular complications at 18-year follow-up. Initial glycemic control was not related to vascular prognosis [47].

The Coronary Artery Calcification in Type 1 Diabetes (CACT1) trial is a prospective study that followed patients with T1D and nondiabetic control subjects free of cardiovascular disease for 6 years. At study entry, insulin resistance was estimated by the euglycemic hyperinsulinemic clamp and coronary artery calcification was measured by electron-beam computed tomography. Insulin resistance predicted the extent and progression of coronary artery calcification in patients with T1D as well as in the nondiabetic subgroup, independently of other risk factors, suggesting that insulin resistance may play an important role in the development of coronary artery calcification [49,60].

The estimation of insulin resistance by HOMA-IR in patients with T1D is inaccurate due to the presence of exogenous insulin that makes meaningless the value of fasting plasma insulin concentration. Clinical features from participants in the Pittsburgh Epidemiology of Diabetes Complications (EDC) study have been used to derive a score that quantifies the severity of insulin resistance in patients with T1D, the estimated glucose disposal rate.

Insulin resistance assessed by the estimated glucose disposal rate at baseline has been associated with increased incidence of cardiovascular disease and mortality in several prospective studies, including the Pittsburgh Epidemiology of Diabetes Complications (EDC) study [48,61,62], the Diabetes Control and Complications Trial (DCCT) [63], the SEARCH CVD study [64], and the Coronary Artery Calcification in Type 1 Diabetes (CACT1) study [65]. In contrast, glycosylated hemoglobin shows no association with incident coronary artery disease [48,61]. Assessing insulin resistance by calculating the estimated glucose disposal rate identifies a subset of patients with T1D who are at highest risk of subsequent vascular disease [63].

Clinical manifestations of insulin resistance have been associated with cardiovascular disease in patients with T1D as well. The EURODIAB study is a large cross-sectional study aimed to examine the prevalence and risk factors of cardiovascular disease in patients with T1D. The prevalence of cardiovascular disease was strongly associated with larger BMI, hypertriglyceridemia and decreased HDL-c, but not with elevated level of glycosylated hemoglobin [66]. In overweight patients with T1D who were asymptomatic for coronary artery disease, coronary artery calcification was evaluated by electron-beam computed tomography performed twice at an interval of 2.7 years. Multiple logistic regression analysis shows that higher insulin dose (suggesting insulin resistance) increased the risk of progression of coronary artery calcification [67].

2.2. Insulin resistance is independently associated with cardiovascular risk in patients with type 2 diabetes

2.2.1. Glycemic control and cardiovascular disease in patients with type 2 diabetes

Several prospective studies have failed to demonstrate a beneficial effect of intensive versus standard glycemic control on the incidence of cardiovascular outcomes in patients with T2D (with the exception of metformin use), including the University Group of Diabetes Program [68–70], the Veterans Affairs Diabetes Feasibility Trial [71], the Veterans Affairs Diabetes Trial [72], the United Kingdom Prospective Diabetes Study (UKPDS) [73], the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [74,75], the Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial [76], and the ADDITION-Europe study (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care) [77].

Accordingly, no beneficial effect of intensive glycemic control on all-cause mortality or death from cardiovascular disease has been observed in several meta-analyses in patients with T2D [78–80].

In the United Kingdom Prospective Diabetes Study (UKPDS), the effect of intensive therapy with metformin (a medication that enhances insulin sensitivity) showed a beneficial effect on diabetes complications. Metformin-treated patients had risk reductions of 32% for any diabetes-related endpoint, including macrovascular complications, compared with the conventional group treated only with diet. Patients allocated metformin had risk reductions of 42% for diabetes-related death, and 36% for all-cause mortality compared to the conventional group [81].

Intensive glucose lowering leads to increased risk of severe hypoglycemic events in patients with T2D, compared to standard therapy [72,74–76,78–80]. In the ADVANCE study, severe hypoglycemia is associated with increased risk of major macrovascular events, death from a cardiovascular cause and death from any cause, after controlling for covariates [82] Similarly, in the Veterans Affairs Diabetes Feasibility Trial, Cox regression analyses show that a lower glycosylated hemoglobin level prior to a cardiovascular event is the only correlate for new cardiovascular events [71]. Like T1D, intensive therapy with insulin in patients with T2D leads to weight gain compared to standard therapy. Weight gain may worsen insulin resistance and cardiovascular risk [73]. Metformin consistently prevents insulin-induced weight gain in patients with diabetes [83].

2.2.2. Insulin resistance is independently associated with cardiovascular disease in patients with type 2 diabetes

Multiples studies provide evidence that insulin resistance by itself is a major determinant of the elevated cardiovascular morbidity and mortality in patients with T2D.

Patients with heterozygous inactivating mutations in the glucokinase gene experience fasting hyperglycemia from birth, but the prevalence of macrovascular complications is similar to the general population and lower than in patients with T2D (4% versus 30%). Patients with T2D are typically insulin-resistant while the degree of insulin sensitivity in patients with heterozygous loss-of-function mutations in the glucokinase gene is comparable to that in

the general population. Cardiovascular risk is not increased in patients with heterozygous inactivating mutations in the glucokinase gene despite lifelong hyperglycemia whereas patients with T2D endure elevated cardiovascular morbidity and mortality regardless glycemic control [84,85].

Metabolic control with metformin (a drug that improves insulin resistance) unlike insulin improves cardiovascular risk in patients with diabetes, suggesting that enhancement of insulin sensitivity, rather than glycemic control, improves diabetes outcomes, including cardiovascular risk [81].

Elevated cardiovascular risk associated to insulin resistance is present for decades before the clinical onset of T2D. Normoglycemic patients with insulin resistance that will develop diabetes have increased cardiovascular risk compared with subjects with normal glucose tolerance [4,34]. In patients with screen-detected T2D, undiagnosed vascular dysfunction is apparent at the time of diagnosis (by screening) [77].

A number of investigations show that insulin resistance by itself is a cardiovascular risk factor in patients with T2D, independently of the diabetes status and other risk factors. Insulin resistance evaluated by insulin tolerance tests is independently related to ischemic heart disease in patients with T2D. T2D patients with ischemic heart disease were more insulin resistant compared to those without coronary disease, after adjustment for confounding variables [86].

In the Verona Diabetes Complications Study, insulin resistance (HOMA-IR) is a strong predictor of both prevalent cardiovascular disease at baseline and incident cardiovascular disease during follow-up in patients with T2D, independently of traditional cardiovascular risk factors [87].

In a prospective study aimed to investigate the impact of insulin resistance (HOMA-IR) on the incidence of vascular events in patients undergoing coronary angiography, baseline insulin resistance predicted the incidence of vascular events after controlling for covariates. Twenty-one percent of the participants in this study have T2D. Additional adjustment for the presence of T2D revealed that HOMA-IR predicted vascular events independent from diabetes status [22].

The effect of insulin resistance (HOMA-IR) on the incidence of cardiovascular events was assessed in subjects with high cardiovascular risk (known coronary heart disease with low HDL-c and low LDL-c) in the Veterans Affairs High Density Lipoprotein Intervention Trial (VA-HIT) study. Patients with insulin resistance had higher relative risk of a cardiovascular event (myocardial infarction, stroke or coronary heart disease death) regardless of the diabetes status compared with subjects without insulin resistance over the 5-year follow-up [21].

The clinical expression of insulin resistance is also independently associated to cardiovascular disease in patients with T2D in cross-sectional and prospective studies [22,38,88–91].

3. Summary

Diabetes is associated with severe vascular damage that is not explained by hyperglycemia or traditional cardiovascular risk factors, such as hypercholesterolemia or smoking. Evidence accumulated for decades identifies insulin resistance as a major cardiovascular risk factor in otherwise healthy subjects and in patients with diabetes either lean or obese independently of other cardiovascular risk factors. Insulin resistance is associated with latent vascular injury before the clinical onset of diabetes. Intensive glycemic control with insulin in patients diabetes compared to conventional care of the disease does not prevent macrovascular complications from occurring and vascular damage continues to develop despite near-normal glycemia. However, improvement of insulin resistance with metformin does reduce diabetes complications and all-cause mortality in patients with diabetes. Intensive insulin therapy induces weight gain that may contribute to worsen insulin resistance. Enhancement of insulin sensitivity has beneficial effects on cardiovascular outcomes in healthy subjects and patients with diabetes.

Conflicts of interest

The authors declare that they have no conflict of interest.

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