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THEN AND NOW

Insulin and cardiovascular disease: biomarker or association?

K. A. M. Jandeleit-Dahm · S. P. Gray

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Abstract In the 1980s prospective studies using whole populations suggested a relationship between insulin and cardiovascular disease, and these studies proposed that both metabolic and haemodynamic factors were associated with cardiovascular events. The initial analysis of the Paris Prospective Study (*Diabetologia* 19: 205–210), published in 1980, showed a positive correlation between insulin and cardiovascular events in healthy middle-aged policemen after a 5 year follow-up. In the Bedford Survey (*Diabetologia* 22: 79–84), also performed in the 1980s, a higher cardiovascular risk was demonstrated in diabetic patients and in those with borderline diabetes; however, in contrast to the Paris Prospective Study, insulin was negatively correlated to cardiovascular endpoints in the Bedford Survey. The initial enthusiasm for insulin as a cardiovascular risk marker was dampened when the 15 year follow-up data of the Paris Prospective Study (*Diabetologia* 34: 356–361) showed that the correlation between insulin and cardiovascular risk subsided with increased duration of follow-up. Despite the fact that hyperinsulinaemia was always strongly associated with other classical cardiovascular risk factors, univariate analyses usually failed to show a strong correlation between insulin and cardiovascular risk. The San Antonio Heart Study (*Diabetologia* 34: 416–422) performed in a bi-ethnic population that included a large proportion of Mexican-American participants again emphasised that insulin resistance may be the underlying factor associated with a cluster of metabolic and haemodynamic abnormalities. However, recently performed meta-analyses that included larger studies have not been able to confirm a critical role for insulin levels in cardiovascular risk. Indeed, it has been suggested that proinsulin or other factors may be better markers than insulin per se.

Keywords Atherosclerosis · Cardiovascular disease · Insulin · Insulin resistance · Risk factors

Abbreviation
I/G ratio Insulin/glucose ratio

K. A. M. Jandeleit-Dahm (✉) · S. P. Gray
Diabetes Complications Division,
Baker IDI Heart and Diabetes Institute,
PO Box 6492, St Kilda Road Central,
Melbourne, VIC 8008, Australia
e-mail: Karin.jandeleit-dahm@bakeridi.edu.au

K. A. M. Jandeleit-Dahm · S. P. Gray
Department of Medicine, Monash University,
Melbourne, VIC, Australia

Introduction

Epidemiological studies have consistently shown that individuals with type 2 diabetes have an approximately twofold increased risk of CHD compared with those free of diabetes [1]. Thus, it has been suggested that not only glucose but also insulin may be marker of cardiovascular risk, particularly early in the time course of diabetes and in states of insulin resistance [2]. In the 1980s, seminal prospective studies were performed where whole populations were subjected to glucose tolerance tests and plasma insulin measurements; these included the Busselton study [3], the Bedford Survey [4], the Helsinki study [5] and the Paris Prospective Study [6]. It was suggested that metabolic factors that occur in type 2 diabetes are not only linked to haemodynamic factors such as hypertension but could also potentially influence cardiovascular risk in an independent manner. This was further supported by the description of the metabolic syndrome [7] demonstrating links among hypertension, obesity, hyperlipidaemia and glucose intolerance in association with elevated circulating insulin levels. In addition, these findings complemented a series of studies published 10–20 years earlier by Stout [8–12], who promoted the idea

that insulin could be involved aetiologically in the development of cardiovascular disease.

Although there was mounting evidence for the link between the metabolic syndrome, diabetes and impaired glucose tolerance on the one hand and cardiovascular disease on the other, the enthusiasm for insulin as an independent risk marker for cardiovascular risk has dampened over the years, particularly in the 1990s, when long-term follow-up studies could not confirm the initial findings. More recent meta-analyses that included multiple studies and a significant number of cardiovascular events, clearly enhancing the power of such analyses, confirmed much weaker associations between cardiovascular risk and fasting or non-fasting insulin levels than had been previously suggested [13]. Furthermore, other markers associated with insulin resistance, such as proinsulin levels, were identified as possibly being better predictors of cardiovascular risk [13]. An overview of the major studies assessing the relationship between plasma insulin and cardiovascular disease is given in Table 1.

Then: insulin—a link between metabolism and cardiovascular complications

In retrospect, a correlation between metabolic and haemodynamic factors leading to cardiovascular disease had already been observed in the 1920s [14]. In a number of rather small studies a link between the prevalence of hypertension and diabetes was suggested. It was hypothesised that hypertension was a prediabetic condition and, vice versa, that elevated blood pressure was associated with a 1.63 increased risk of diabetes [15]. The Whitehall Study [16], published in the 1980s, looked at the relationship between glucose tolerance and cardiovascular disease in 19,000 civil servants aged over 40 years who were assessed for the presence of hypertension and glucose intolerance. This study showed that men with impaired glucose tolerance (top 2% of glucose distribution) had a similar risk of dying from CHD compared with diabetic patients after 5 years of follow-up. These participants in the upper 5% of the glucose distribution had a doubling of CHD mortality at 7.5 years, independent of other risk factors. As in the Framingham study [17–19], the excess mortality could not be explained by age, blood pressure, cholesterol and cigarette smoking alone. Blood pressure appeared to be an important predictor of CHD mortality in people with impaired glucose tolerance, further suggesting a link between metabolic and haemodynamic disorders.

In the Busselton study [3], also performed at that time, the general population of the small town of Busselton in Western Australia underwent a glucose tolerance test (n= 3,390, 91% of the population). This study showed that 1 h post-load glucose levels were associated with increased 6 year morbidity and 12 year mortality rates from CHD. However, only in one of the six age- and sex-specific groups was there a significant association between insulin and cardiovascular events, namely, men aged between 60 and 69 years. As in the Framingham prospective study, the risk indices for age, LDL-cholesterol, low HDL-cholesterol, blood pressure and cigarette smoking were common and similar in diabetic and non-diabetic participants and the increased cardiovascular disease risk could not be explained by those conventional risk factors alone. This study also suggested that women with diabetes or borderline diabetes had a higher risk for cardiovascular disease than men with similar metabolic control.

In subsequent multivariate analyses performed after 13 years of follow-up there was, unexpectedly, a negative correlation between insulin and all-cause mortality in men aged 40–59 years and a positive correlation with cancer in men aged 60–79 years [20].

The Paris Prospective Study was performed at a similar time but included healthy policemen and specifically investigated the relationship between plasma insulin levels and the incidence of myocardial infarction and CHD mortality [6]. Over 7,000 healthy, non-diabetic working men, aged between 43 and 54 years, were investigated and followed for an average of 63 months. These individuals were initially free from cardiovascular disease and 128 new CHD events (non-fatal myocardial infarction and coronary-related deaths) were detected during the study period. The annual risk was assessed by multivariate modelling including age, serum cholesterol and triacylglycerol, blood pressure, smoking, obesity, plasma glucose and insulin, both fasting and 2 h after a 75 g oral glucose load. The most important finding of the study was that fasting insulin and the fasting insulin/glucose (I/G) ratio were positively associated with cardiovascular risk, independently of other factors. The same variables were also positively related to risk after a 2 h glucose load, but their contribution was not significant in the multivariate analysis. When the fasting I/G ratio was presented in quintiles, the highest risk for cardiovascular death was reported in the highest quintiles (4 and 5; >13 mU/g) of plasma insulin concentrations. There was a positive correlation between insulin and cardiovascular events in the study, but the relationship between glucose and cardiovascular risk was negative, suggesting that for any given glucose level there was an excess of insulin, consistent with insulin resistance being a key variable in the prediction of CHD.

Other authors have also suggested that the I/G ratio may be a useful tool to assess insulin resistance. Individuals who suffered a myocardial infarction had a higher I/G ratio than controls [21]. Santen et al observed a higher fasting I/G ratio in diabetic patients with atherosclerosis compared with

Table 1 Overview of major studies assessing the relationship between plasma insulin and cardiovascular disease

Study	Diagnostic criteria	Follow-up	Findings for insulin and cardiovascular disease
1982:			
Bedford Survey Healthy, borderline diabetic patients and type 2 diabetic patients ~200 in each group, men and women	Glucosuria, then 50 g OGTT 2 h >11 mmol/l (200 mg/100 ml); normal: 2 h <6.7 mmol/l (120 mg/100 ml)	1962–1972 (10 years)	Borderline diabetes confers higher relative cardiovascular risk in women than in men Other independent predictive factors: Age at entry, systolic BP and smoking 2 h plasma insulin after 50 g glucose load was inversely related to angina and incidence of any cardiac event
1980:			
Paris Prospective Study 7,264 non-diabetic, healthy participants aged 43–54 years, all male	75 g OGTT	63 months (5 years)	Predictive: fasting I/G ratio Highest risk with insulin quintiles 4 and 5 Fasting I/G ratio >13 mU/g
1991:			
Paris Prospective Study 6,903 middle-aged male and 125 non-insulin treated diabetic patients aged 43–54 years, all male	75 g OGTT	15 year follow-up	Predictive: 2 h post-load insulin as a categorical variable, or highest quintile of the 2 h insulin, but not fasting insulin Other predictors: systolic BP, cigarette smoking, cholesterol
1990:			
San Antonio Heart Study, 2,930 participants, mean age 42.9 years (43% men, 68% Mexican-American)			Prevalence: Obesity 54.3% (in its isolated form: 29%) Type 2 diabetes 9.3% – isolated 1.3% IGT 11.1% – isolated 1.8% Hypertension 9.8% – isolated 1.5% HT 10.3% – isolated 1.0% HC 9.2% – isolated 1.7% Major overlap between all six disorders – each disorder characterised by hyperinsulinaemia (fasting and 2 h)

IGT, impaired glucose tolerance; HT, hypertriacylglycerolaemia; HC, hypercholesterolaemia

those without atherosclerosis [22]. Furthermore, highly significant associations were found between the I/G ratio and triacylglycerol as well as obesity [23]. The relationship of the I/G ratio with triacylglycerol could not be analysed in the Paris Prospective Study because lipids and, in particular, triacylglycerol and HDL-cholesterol were not measured.

Other studies have also suggested a positive correlation between insulin levels and cardiovascular risk. In the Helsinki study glucose tolerance tests were performed in 1,059 male policemen aged 35–59 years at baseline and repeated after 5 years. Pyorala et al [5, 24] found that fasting and the 1 h and 2 h post-load plasma insulin values were associated with an increased incidence of CHD death and non-fatal myocardial infarction. In this study, the 2 h value appeared to be a better predictor than the fasting level. However, after a further 9.5 years follow-up, only the upper part of the distribution of the 1 and 2 h post-load insulin levels, but not the fasting levels, was significantly associated with the combined endpoint. Consistent with these findings emphasising post-glucose-loading serum insulin levels, Welborn and Wearne observed in the Busselton study an association between the 1 h post-load insulin level and CHD incidence in men, but not in women [3].

Based on the studies described in the 1980s, it was suggested that insulin could play an independent role as a risk factor for CHD; however, the evidence remained controversial. Other studies, such as the Gothenburg study [25], the Edinburgh study [26] and a study in Pima Indians [27] (a population characterised by a high incidence of hyperinsulinaemia and progression to type 2 diabetes), did not report positive associations.

Another large prospective cohort study performed in the 1980s was the Bedford Survey, in which glucose tolerance tests were performed in the whole adult population of the

English town of Bedford (n=24,701) [4]. Ten-year mortality rates were compared between newly diagnosed diabetic patients, individuals with borderline diabetes and normoglycaemic controls. The three groups varied significantly in age. Age-corrected mortality rates were highest in the diabetic group, followed by the borderline diabetic participants. Using multiple logistic statistical methods, borderline diabetic women had a significantly increased odds ratio of dying from all deaths vs control participants. The diabetic group also had a higher risk of dying than the borderline diabetic group, but the small number of participants probably resulted in a failure to reach statistical significance. It was concluded that borderline diabetic women had a greater increase in mortality compared with borderline diabetic men.

In the borderline diabetic patients, raised systolic BP was the major risk factor for myocardial infarction. The findings for plasma insulin concentrations were negative. Indeed, plasma insulin levels were lowest in individuals who subsequently developed angina with respect to cardiovascular disease and in the total group sustaining any cardiac event, as assessed by ECG change and/or angina and/or possible infarction, thus suggesting a negative relationship between insulin and cardiovascular risk. Similar data were also obtained for CHD death. In a multiple regression analysis in relation to coronary morbidity, BMI was independently and significantly predictive of angina. Multiple logistic analysis relating to mortality showed that the major predictive factors for mortality were age, cigarette smoking and systolic blood pressure, all approaching 5% significance, but circulating insulin concentrations failed to reach statistical significance.

Unfortunately, the long-term follow-up of the Paris Prospective Study 15 years later could not confirm the initial positive results observed with respect to insulin. The 15 year follow-up included 6,903 middle-aged male participants aged 43–54 years who were compared with 125 non-insulin-treated diabetic participants [28]. The baseline variables were tested as predictors of death from CHD using a Cox regression analysis. The predictors of death from CHD were systolic blood pressure, number of cigarettes smoked per day and cholesterol levels, but there was no correlation with fasting insulin. However, there was a positive correlation between incidence of CHD and the 2 h post-load insulin level, but only when entered as a categorical variable with a cut-off of 452 pmol/l (the lower limit of the fifth quintile of the distribution). Although participants who died from CHD had higher plasma insulin levels (both fasting and 2 h post-load), only the last quintile of the 2 h post loading value was predictive for cardiovascular events when using categorical variables.

In the Multiple Risk Factor Intervention Trial for the Prevention of Coronary Heart Disease (MRFIT) study, fasting serum insulin levels were measured in men at high risk for CHD and compared with matched healthy controls. Mean serum insulin levels were almost identical in patients and controls [29]. These studies could not confirm the initial positive results with respect to insulin as a biomarker for cardiovascular disease. Thus, while hyperinsulinaemia was associated with a range of other factors, summarised as the metabolic syndrome, suggesting that insulin resistance was the underlying pathology leading to a cluster of cardiovascular risk factors, the evidence for plasma insulin being an independent biomarker for cardiovascular disease was either weak at best or non-existent, in particular after longer follow-up periods [7].

The San Antonio Heart Study [30] was a population-based survey of 2,930 individuals with a large component of Mexican-Americans (43% men, 68% Mexican-American). In this population, prevalence rates of obesity were very high at 54.3%, and prevalence rates for type 2 diabetes (non-insulin dependent) were 9.3%, for impaired glucose tolerance 11.1%, for hypertension 9.8%, for hypertriacylglycerolaemia 10.3% and for hypercholesterolaemia 9.2%. The prevalence of each of these conditions in their isolated form (without the other five) was 29% for obesity, 1.3% for type 2 diabetes, 1.8% for impaired glucose tolerance, 1.5% for hypertension, 1.0% for hypertriacylglycerolaemia and 1.7% for hypercholesterolaemia. The large differences in prevalence between isolated and mixed forms indicate a major overlap among the six disorders in multiple combinations. In its isolated form each condition was characterised by hyperinsulinaemia (both fasting and 2 h after oral glucose), suggesting the presence of insulin resistance. In addition, in any isolated condition most of the other variables of the sextet were still significantly altered when compared with 1,049 normal participants. Individuals who presented with one or another disorder (64%) showed marked fasting and post-glucose hyperinsulinaemia, which was associated with higher BMI, waist-to-hip ratio, fasting and post-glucose glycaemia, raised systolic and diastolic BP, elevated serum triacylglycerol and total cholesterol, and lower HDL-cholesterol levels.

The authors of the San Antonio Heart study suggested that insulin sensitivity, glucose tolerance, blood pressure, body fat mass distribution and serum lipids are a network of mutually interrelated functions and that the insulin resistance syndrome underlies each of the six disorders that carry an increased risk for coronary artery disease, at least in the population studied, which has a high metabolic and cardiovascular disease burden. It was, however, noted that this population is not representative of other populations because of its unique composition, including a high proportion of Mexican-Americans, who have a high prevalence of the metabolic syndrome and insulin resistance. Thus, findings obtained from this survey cannot easily be translated to other populations.

Why is insulin not a good biomarker for cardiovascular disease?

Our current knowledge about the role of insulin in cardiovascular disease is based on larger meta-analyses and a better understanding of the pathophysiology of insulin in vascular disease. A number of more recent studies have added support to a link between insulin and cardiovascular disease with a positive correlation between insulin and cardiovascular events reported, such as in the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) study [31]. In this study fasting insulin levels above a cut-off of 271 pmol/l (39 μU/ml) were associated with a highly significant 31% increase in risk of cardiovascular events [31]. Similar results have been obtained by Ruige et al in 1998, including data from 12 prospective studies involving 800 cardiovascular endpoints [32]. In this meta-analysis, the authors reported a relative risk of 1.17 for a 50 pmol/l increase in fasting insulin and of 1.16 for a 250 pmol/l increase in non-fasting insulin concentrations. Another meta-analysis included data from 11 prospective trials and reported 400 vascular deaths in western European countries [33]. That analysis showed a relative risk of 1.54 in men and 2.66 in women for cardiovascular disease with higher insulin levels. The most recent meta-analysis included 19 studies with less heterogeneity and analysed three different insulin variables: fasting and non-fasting insulin and proinsulin levels. It included only Western populations and reported 3,600 incident cases of non-fatal myocardial infarction and death. It was concluded that the association between insulin and cardiovascular events is weaker than previously suspected. It was suggested that circulating levels of proinsulin may be more strongly associated with CHD events [13].

Effects of insulin on the vasculature

Insulin resistance is the common denominator for at least six conditions associated with increased cardiovascular risk. Hyperinsulinaemia could also be the common basic cellular defect relevant to all these conditions. The direct role of insulin in mediating vascular injury remains controversial. People who develop atherosclerosis have higher plasma insulin levels. Furthermore, the arterial wall is an insulin-sensitive tissue [34]. Insulin promotes the proliferation and migration of vascular smooth muscle cells, inhibits lipolysis and increases the synthesis of cholesterol, phospholipids and triacylglycerol (Fig. 1). These processes also occur in the vascular wall and lead to the accumulation of lipids there, resulting in attraction of inflammatory cells with subsequent promotion of inflammation and extracellular matrix remodelling—all key features of atherosclerosis development. More recently, it has also been shown that insulin promotes macrophage foam cell formation [34, 35].

Pathway-selective insulin resistance has also been implicated in the directly damaging effects of insulin on the vascular wall. Diabetes and obesity are associated with selective insulin resistance in the phosphatidylinositol-3-kinase signalling pathways, which leads to reduced synthesis of nitric oxide, impaired metabolic control and compensatory hyperinsulinaemia; however, insulin signalling via extracellular signal-regulated kinase-dependent pathways is unaffected, leading to abnormal vascular reactivity and angiogenesis [36].

Furthermore, elevated insulin could indirectly affect the vasculature by leading to hepatic VLDL overproduction. Hyperinsulinaemia can also raise blood pressure by a variety of mechanisms, including salt and water retention and sympathetic adrenergic activation. However, it has also been suggested that insulin may have beneficial effects on vascular function and could be anti-inflammatory [37, 38].

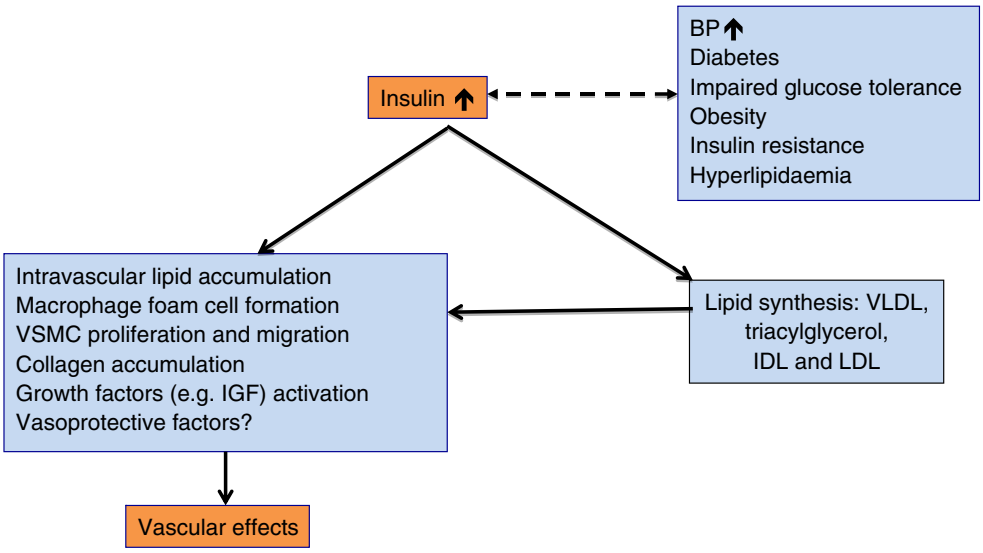

Fig. 1 Proposed direct and indirect vascular effects of insulin. IDL, intermediate-density lipoprotein; VSMC, vascular smooth muscle cell

Indeed, early administration of exogenous insulin has been considered to be a controversial approach because of the potential negative effects of insulin on the vasculature. However, the results of the recently published Outcome Reduction with Initial Glargine Intervention (ORIGIN) study showed that early treatment of diabetic patients with exogenous insulin glargine (A21Gly,B31Arg,B32Arg human insulin) was neutral on cardiovascular outcomes after a 6.2 year study follow-up [39]. Furthermore, it has been suggested that insulin assays also measure other insulin-like molecules, in particular in individuals with increasing glucose intolerance, and that these insulin-like molecules, including proinsulin, may indeed show stronger correlations with cardiovascular events than insulin itself [40–42].

In summary, the exact relationship between insulin and cardiovascular disease is still unclear. Studies in the 1980s that discovered a link between metabolic disturbances and cardiovascular disease emphasised a role for insulin resistance as an accelerator of cardiovascular risk, and suggested a role for insulin as an independent risk factor, although the evidence was controversial. Subsequent studies have, however, been disappointing in general, and long-term follow-up studies, including larger cohorts, have not supported a critical role for insulin as a biomarker in cardiovascular disease. Recent meta-analyses suggest a much weaker role for insulin as a cardiovascular biomarker than previously predicted. Whereas insulin itself may not be the ideal biomarker, other factors related to insulin resistance, such as proinsulin, the proinsulin/insulin ratio or insulin-like molecules, may be more relevant markers of cardiovascular disease risk [32, 33].

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