Insulin and atherosclerosis: How are they related?

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Abstract

The relationship between insulin and atherosclerosis is complex. People with type 2 diabetes are affected by three main glycaemic disorders: chronic hyperglycaemia; glycaemic variability; and iatrogenic hypoglycaemia. In addition to this triumvirate, the diabetic condition is characterized by lipid disorders, chronic low-grade inflammation and activation of oxidative stress. All these associated disorders reflect the insulin-resistant nature of type 2 diabetes and contribute to the development and progression of cardiovascular (CV) diseases. By both lowering plasma glucose and improving the lipid profile, insulin exerts beneficial effects on CV outcomes. In addition, insulin has several pleiotropic effects such as anti-inflammatory, antithrombotic and antioxidant properties. Insulin per se exerts an inhibitory effect on the activation of oxidative stress and seems able to counteract the pro-oxidant effects of ambient hyperglycaemia and glycaemic variability. However, insulin actions remain a subject of debate with respect to the risk of adverse CV events, which can increase in individuals exposed to high insulin doses. Evidence from the large-scale, long-term ORIGIN trial suggests that early implementation of insulin supplementation therapy in the course of glycaemic disorders, including type 2 diabetes, has a neutral impact on CV outcomes compared with standard management. Thus, the answer to the question “What impact does insulin have on atherosclerosis?” remains unclear, even though it is logical to deduce that insulin should be initiated as soon as possible and that small doses of insulin early on are better than higher doses later in the disease process.

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Résumé

Insuline et athérosclérose. Quelle relation ?.

La relation entre insuline et athérosclérose est complexe. Les diabétiques de type 2 présentent trois désordres glycémiques majeurs : une hyperglycémie chronique, des fluctuations glycémiques et des hypoglycémies iatrogènes. En parallèle, les états diabétiques sont caractérisés par des désordres lipidiques, un état inflammatoire de faible niveau et une activation du stress oxydatif. Toutes ces altérations, qui sont la conséquence d’une insulinorésistance inhérente au diabète de type 2 contribuent activement au développement et à la progression des maladies cardiovasculaires. L’insuline réduit le risque de maladies cardiovasculaires en diminuant la glycémie et en améliorant le profil lipidique. Elle agit également par des effets pleiotropes, anti-inflammatoires, antithrombotiques et anti-oxydants. L’insuline per se inhibe l’activation du stress oxydatif et semble capable de contrebalancer l’effet pro-oxydant de l’hyperglycémie ambiante et de la variabilité glycemique. Toutefois, l’insuline peut avoir des effets délétères, en particulier chez les sujets recevant de fortes doses d’insuline. Les résultats de l’étude ORIGIN, réalisée sur une grande échelle et sur le long terme, suggèrent que l’insuline utilisée précocement dans les troubles de la glycérégulation, y compris chez les diabétiques de type 2, a un comportement neutre sur le devenir cardiovasculaire lorsqu’elle est comparée à un traitement standard. La réponse à la question : « Quel est l’impact de l’insuline sur l’athérosclérose ? » reste en suspens, même s’il est logique de penser que l’insuline devrait être initiée le plus tôt possible et que de petites doses utilisées précocement sont préférables à de fortes doses prescrites tardivement.

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At this time there is cogent evidence that frank type 2 diabetes is characterized by an increased risk for cardiovascular (CV) diseases. From a ‘glucocentric’ point of view, the three main contributors to the enhanced risk for adverse CV
outcomes are chronic ambient hyperglycaemia, glycaemic variability and the occurrence of iatrogenic hypoglycaemic episodes [1]. In addition, it is well recognized that the quality of glucose homeostasis steadily deteriorates throughout the natural course of the disease [2]. The progression towards more severe stages leads to the initiation of insulin treatments when oral hypoglycaemic agents (OHAs) are deemed to have failed to achieve and sustain a satisfactory level of glycaemic control [3]. Because most individuals at this stage of type 2 diabetes are obese and insulin-resistant, the daily insulin doses needed are usually high when treat-to-target protocols are implemented [4]. This observation raises the question of whether the use of insulin, especially at high doses that result in hyperinsulinaemia, could have a negative influence on the risk factors that contribute to the pathogenesis of atherosclerosis in people with type 2 diabetes.

1. Overview of the pathogenesis of atherosclerosis in diabetes

In addition to glycaemic alterations, it has been demonstrated that many other putative CV risk factors could play a substantial role in facilitating the development and progression of macrovascular complications in type 2 diabetes (Fig. 1). From a general point of view, all states of insulin resistance present in such diseases as obesity and type 2 diabetes are frequently associated with dyslipidaemia [5] and chronic low-grade inflammation [6].

1.1. Role of insulin resistance and inflammatory processes

While considering the impact of insulin use on these parameters, it should be remembered that one of the pivotal disorders in type 2 diabetes is a defect in insulin action at multiple sites, including muscle, liver and adipose tissue [7]. In peripheral target tissues, insulin stimulates glucose uptake and more generally regulates the whole body’s glucose homeostasis through a metabolic cascade that is initiated by insulin binding to its receptor, which is then activated. The main steps in this activation include phosphorylation of several insulin receptor substrates (IRS) that, in turn, leads to downstream activation of phosphoinositide-3 (PI3) kinase and Akt [8,9]. This signaling sequence ultimately results in glucose transport to the cells and stimulation of multiple intracellular metabolic processes, but this metabolic pathway is altered in insulin-resistant type 2 diabetes, thereby leading to a decrease in glucose transport.

However, another pathway — the mitogen-activated protein (MAP) kinase pathway that also proceeds from activation of the insulin receptor — remains responsive to insulin even in subjects who are insulin-resistant [9,10]. As a consequence, this pathway remains stimulated or even overstimulated in diabetic patients who are insulin-resistant in the presence of compensatory endogenous chronic hypersecretion of insulin in response to decreased insulin sensitivity. This alternative pathway can also be overstimulated by exposure to exogenous insulin, a situation that becomes more prevalent when high doses of insulin are required to overcome insulin receptor defects to achieve the recommended glycaemic targets. The MAP kinase pathway is involved in inflammation, cell growth and proliferation, and also in furthering the development and/or progression of atherosclerosis [9]. Therefore, excessive stimulation of this pathway via endogenous or exogenous hyperinsulinaemia can play a major role in the pathogenesis of diabetic CV complications [10].

Type 2 diabetes is also a recognized chronic inflammatory condition [6] and as such can result in a number of adverse consequences. There is little doubt that most inflammatory markers/cytokines that are generated and released during an inflammatory process exert deleterious effects by inducing a state of insulin resistance or its aggravation if already pre-existing. In addition, these inflammatory markers increase the potency of platelets to aggregate, and result in endothelial cell dysfunction and further damage to the vascular tree [11] in people with diabetes. These markers include nuclear factor-kappa B (NF-kB), matrix metalloproteinases, intracellular adhesion molecules (ICAMs), selectin, monocytic chemotactic protein-1 (MCP-1), plasminogen activator inhibitor (PAI)-1 and C-reactive protein (CRP). In diabetes and more generally in obese individuals, especially those with the metabolic syndrome, it has been demonstrated that circulating concentrations of these substances are elevated [12]. Such an inflammatory state is present in both non-diabetic obese subjects and patients with type 2 diabetes and thus represents the ‘common denominator’ of both syndromes characterized by a state of insulin resistance.

1.2. Role of dysglycaemia considered as a whole

There are many reasons to think that dysglycaemia may be central to the activation and overexpression of such inflammatory markers. Glycaemic dysregulation can act through its two main components, sustained chronic ambient hyperglycaemia and glycaemic variability. The latter refers to glucose fluctuations as reflected by the peaks and troughs. Glycaemic peaks, especially in type 2 diabetes, usually correspond to post-meal glucose excursions, while troughs can reflect low blood glucose...
and a risk of hypoglycaemia. As a consequence, iatrogenic hyperglycaemic episodes, especially those that are recurrent, can be considered an additional component of the glucose ‘triumvirate’ [1].

Ambient hyperglycaemia is also a key player in the pathogenesis of micro- and macrovascular diseases in both type 1 and type 2 diabetes. Causality has been widely established by at least two landmark studies: the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes [13]; and the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes [2,14]. The central role of ambient hyperglycaemia and the legacy of the deleterious effects of prolonged periods of sustained hyperglycaemia were demonstrated by studying the macrovascular outcomes during the post-trial periods of the two above-mentioned studies [15,16]. In addition, excess protein glycation due to increased glucose exposure [17,18] has been demonstrated to activate oxidative stress and induce a pro-thrombotic state [1,19]. As the proinflammatory, pro-oxidant and prothrombotic states are all interrelated, these mechanisms may be contributing to the adverse outcomes observed during hyperglycaemia in people with diabetes and acute coronary syndrome [20].

1.3. Specific role of glucose fluctuations

Glycaemic variability has also been associated with the activation of oxidative stress [21]. In 2005, Ceriello [22] demonstrated that postprandial glucose excursions activated oxidative stress in patients with type 2 diabetes, depicting “postprandial hyperglycaemic spikes” as “dangerous postprandial waves”. During either postprandial periods or acute hyperglycaemic surges, several key risk factors for CV diseases can be over-expressed. Acute hyperglycaemia induces the overproduction of superoxide anions via the mitochondrial electron-transport chain that results in acute endothelial dysfunction through the production of highly reactive oxygen species (ROS) and other vasculotoxic oxidants, including hydrogen peroxide and peroxynitrite molecules, along with the activation of p53 in endothelial cells, which can also contribute to atherosclerosis [23,24]. In addition, in vitro data have suggested that intermittent high glucose enhances apoptosis in endothelial cells [25]. Such observations were confirmed and more generally extended when it was demonstrated that, in non-insulin-treated patients with type 2 diabetes, the 24-h urinary excretion rate of 8-iso-prostaglandin (PG) F2-alpha, one of the most reliable markers of activation of oxidative stress, was strongly correlated with the mean amplitude of glucose excursions (MAGE) index, a well-recognized indicator of same-day glucose variability [21]. These results were in agreement with those published by Ceriello et al. [25] two years later, using the glucose clamp technique at different levels of glucose concentrations in patients with type 2 diabetes. These authors demonstrated that both upward and downward swings of glucose concentrations were associated with parallel oscillating plasma levels of nitrotyrosine, another marker of activation of oxidative stress. More recently, the present authors reported that, in non-insulin-treated type 2 diabetes, the 24-h urinary excretion rate of 8-iso-PGF2-alpha depended equally on ambient hyperglycaemia and glycaemic variability, as estimated by HbA1C levels and MAGE indices, respectively [19].

2. Overview of atherosclerosis pathogenesis with a particular focus on insulin: is insulin an anti- or proatherogenic hormone?

2.1. Protective effects of insulin

In 2010, the present authors reported the results of a cross-sectional study that compared three groups of subjects with type 1 or type 2 diabetes treated with either OHAs or a regimen combining oral antidiabetic drugs (OADs) in combination with insulin [19]. The data indicated that the 24-h urinary excretion rates of 8-iso-PGF2-alpha were only raised in those treated with OHAs and were within the normal range in the two groups treated with insulin. These results were observed despite the fact that the glycaemic variability estimated by the MAGE index was significantly higher in those using insulin treatment than in those taking oral therapy alone. In addition, in a subgroup of patients with type 2 diabetes, 24-h urinary excretion rates of 8-iso-PGF2-alpha were evaluated at baseline while being treated with OHAs and at several months or years after initiation of supplementary insulin therapy. From highly elevated levels before the initiation of insulin, a drastic reduction was observed in the 24-h urinary excretion rates of 8-iso-PGF2-alpha to within the normal range with the introduction of insulin therapy [19]. Such results strongly suggest that insulin per se exerts an inhibitory effect on the activation of oxidative stress and is able to overcome the pro-oxidant effect of glycaemic variability. This observation also suggests that it is now time to reevaluate the effects of insulin especially in type 2 diabetes while also emphasizing the complexity of the relationship.

From an analysis of the results obtained in vitro and in clinical studies, there are many reasons to consider that insulin is an anti-inflammatory, antioxidant, antithrombotic and antiatherogenic modulator [11]. Indeed, in vitro studies show that insulin suppresses the expression of ICAM-1, MCP-1 and NF-kB binding in human endothelial cells. In obese subjects, a low-dose insulin infusion (2 U/h) suppressed ROS generation. Plasma concentrations of ICAM-1, MCP-1, matrix metalloproteinases and PAI-1 also fell significantly when insulin was infused at rates permitting plasma glucose concentrations to be maintained at near-normal and stable levels.

Clinical trials using relatively low doses of insulin therapy in subjects who had experienced acute myocardial infarction or coronary artery bypass graft (CABG) surgery, or been admitted to an intensive care unit for an acute coronary syndrome, have shown that insulin exerts anti-inflammatory, antioxidant and antithrombotic actions independently of any improvement in plasma glucose concentration [20]. Analysis of the Diabetes Insulin Glucose in Acute Myocardial Infarction (DIGAMI 1 and 2) studies [26,27] provided results that differed slightly from one study to the other. In the DIGAMI 1 study [26], the long-term survival rate was found to be better in those who received treatment with insulin than in those who were not. In contrast, the DIGAMI 2 study [27], which acutely introduced long-term
insulin treatment, did not improve survival rates in type 2 diabetes following myocardial infarction compared with conventional management at similar levels of glycaemic control. In that study, the most powerful prognostic predictor for improved survival was the control of glucose concentration. On bringing together the results from the two DIGAMI studies [26,27], it appears that the quality of diabetic control is an important factor in reducing long-term mortality after myocardial infarction. This suggests that regimens of insulin therapy should be appropriately intensified to achieve optimal glycaemic control when the defined glycaemic targets cannot be obtained with conventional treatments. In addition, a recent study also pointed out that, with everything else being equal, lower death rates were observed when the control of glycaemic variability was improved in subjects admitted to an intensive care unit following an acute illness [28].

All of these studies indicate that both the appropriate delivery of insulin and intensified control of glycaemic disorders are of key importance in improving survival rates. However, it is difficult to separate the respective contributions of these factors, as intensive metabolic control is usually only obtained by means of intensified insulin therapy.

2.2. The controversy

Clinical trials of type 2 diabetes treated with long-term insulin therapy have demonstrated that, despite a similar degree of glycaemic control (HbA1c), a reduction in glycaemic variability does not result in any additional benefit in reducing the risk of CV events. Indeed, this was demonstrated by the results of the HEART2D trial [29]. This study was initially designed to determine whether control of basal hyperglycaemia or postprandial hyperglycaemia is better for reducing CV outcomes in those with type 2 diabetes and a history of myocardial infarction. The participants were assigned to either a basal insulin strategy that targeted fasting and interprandial glycaemia or an insulin regimen with three daily injections of a rapid-acting insulin analogue at premeal times to target postprandial glucose excursions. Although similar lowering effects on HbA1c were achieved with the two insulin regimens, no difference in the incidence of CV events was detected between them despite the fact that the prandial insulin group had lower postprandial glycaemia compared with the basal insulin group on interim analysis when the study was halted after a mean follow-up of 2.7 years.

The overall negative results of the HEART2D study led the authors to conclude that better control of postprandial excursions and perhaps also of glucose variability did not provide any benefit in terms of macrovascular outcomes. A post-hoc analysis of the HEART2D study was then conducted by Siegelaar et al. [30] to assess whether glycaemic variability exerted any influence or not on macrovascular outcomes. While the original study results appeared to indicate that glycaemic fluctuations differed between prandial and basal regimens at the end of the study, glycaemic variability was not reported [29]. When Siegelaar et al. [30] looked at some well-recognized indices of glycaemic variability, they could find no significant differences between the two treatment arms. However, when glucose variability was assessed by changes in mean absolute glucose (MAG; a new controversial marker of glycaemic variability), this was found to be lower in the prandial-insulin vs. basal-insulin treatment group. The authors suggested that targeting glycaemic variability with a prandial insulin strategy was not beneficial for reducing the risk of secondary CV events.

These results therefore raise the question of how glycaemic variability can be, on the one hand, a potent activator of oxidative stress in non-insulin-treated type 2 diabetic patients while being, on the other hand, unable to exert any significant influence on CV outcomes in those with diabetes as soon as they are treated with insulin. Nevertheless, it should be mentioned that the HEART2D study failed to reach the predefined 2.5 mmol/L difference in postprandial glucose between the two strategies, whereas the NAVIGATOR study [31] also did not help to elucidate the impact of postprandial glucose because of methodological limitations.

2.3. An attempt to bridge the controversy

The answer to the above question may reside in the results reported in 2010 [19] that strongly suggested that insulin exerts an independent inhibitory effect on the activation of oxidative stress. Thus, the risk of CV complications in diabetes can be described in a glucocentric model in which three glycaemic disorders (hyperglycaemia during basal and postprandial periods, and acute fluctuations) and two pathophysiological mechanisms (excess glycation as assessed by HbA1c and the generation of oxidative stress) are involved. In patients with type 2 diabetes treated with OHA alone, ambient and postprandial hyperglycaemia both contribute to increases in HbA1c and therefore to excess glycation, whereas the activation of oxidative stress depends on both HbA1c and glycaemic variability.

The resulting effect of all these factors is a risk of CV complications as depicted by a diagonal arrow through a geometric cube (Fig. 2) in which the three-dimensional coordinate axes are basal, postprandial glucose and glucose fluctuations [1]. In patients treated with insulin, it is suggested that the risk of complications is restricted to increased levels of HbA1c and an excess of glycation, as the deleterious effects of acute glucose fluctuations can be neutralized by exogenous insulin provided that iatrogenic hypoglycaemic episodes are avoided [32–34]. Such a model permits, to a certain degree, a way to bridge the controversy and explain why glycaemic variability appears to play only a minor role in patients treated with insulin even when marked glucose surges are observed.

3. Potential clinical consequences of an insulin strategy in type 2 diabetes

The influence of insulin on the CV complications of diabetes remains a subject of debate [35] as intensive insulin regimens using high doses of insulin can lead to increased CV morbidity and mortality in high-risk individuals with type 2 diabetes. Even though the main benefit of insulin therapy is the restoration and maintenance of near-normal glycaemia in patients with type 2 diabetes, insulin at elevated doses can promote oxidative stress [9,10]. Recent work by our team demonstrated that, in
Fig. 2. A three-dimensional model to illustrate the pathophysiological impact of excess glycation and activation of oxidative stress on the risk of diabetic complications (dark solid arrow). The contributions of components of dysglycaemia, such as basal hyperglycaemia (BHG), postprandial hyperglycaemia (PPHG) and the mean amplitude of glycaemic excursions (MAGE) are indicated on the x, y and z axes, respectively. The model differs according to whether diabetic patients are treated with either oral hypoglycaemic agents (OHAs) alone (left) or insulin (right) [1].

patients with type 2 diabetes treated with insulin, the 24-h urinary excretion rates of 8-iso-PGF2-alpha were only within the normal range in those receiving a daily dose of insulin inferior to 0.4 U/kg bodyweight per day [36]. In contrast, the urinary excretion rates of this metabolite were raised in those treated with daily doses superior to 0.4 U/kg bodyweight per day. This means that it is not unreasonable to suggest that the correction of endogenous insulin deficiency by relatively small insulin doses could achieve near-normal levels of oxidative stress and thus limit the risk of ensuing vascular complications. In contrast, relatively high doses of insulin do not appear to have any antioxidant effects. This suggests that insulin could be a ‘bifaceted’ hormone with beneficial antiatherogenic effects at doses resulting in near-physiological circulating insulin levels, but with deleterious proatherogenic actions when the insulin doses are high enough to result in supraphysiological (pharmacological) levels.

Such a bimodal effect of insulin highlights several issues. First, the relationship between insulin and oxidative stress in type 2 diabetes is complex and warrants further studies. Second, it is reasonable to suggest that insulin therapy be initiated early in the course of the disease and that smaller doses given earlier are better than higher doses used later in the course of the disease. These conclusions are in agreement with the fact that the debate surrounding the relative merits of the antiatherogenic and proatherogenic effects of insulin across the spectrum of type 2 diabetes still remains wide open [10,11]. Although the antiatherogenic effects of insulin are supported by numerous studies [11,19,20], there are other published reports that highlight proatherogenic effects [10]. As a consequence and as indicated above, the latter effect of insulin needs to be tested in the setting of randomized clinical trials. As already mentioned in this report, overexposure to either endogenous or exogenous insulin can be overstimulative due to the production of metabolic signals through the MAP kinase pathway that are involved in activation of the vascular atherosclerosis process. In June 2012 at the American Diabetes Association (ADA) meeting in Philadelphia, PA, the results of the ORIGIN trial, designed to determine whether early basal insulin treatment by insulin glargine in high-risk individuals with newly diagnosed type 2 diabetes or prediabetes is a crucial CV risk determinant [37], were presented and subsequently published [38]. This question is debated in the final section of this review.

4. Does the ORIGIN trial help to simplify our understanding of the relationships between insulin and atherosclerosis?

Considered as a whole, the results of the large-scale long-term ORIGIN trial showed no differences in the rates of CV events between basal insulin glargine and standard-care treatment arms throughout the median 6.2 years follow-up [38]. The lower glucose exposure observed in the glargine group was represented by a 0.3% stable difference in HbA1c between the two arms. This difference would normally have resulted in a lower rate of CV events in a high-risk population.

The lack of difference poses several interesting relevant questions. First, it is important to know whether the participants recruited into the ORIGIN trial with a mean HbA1c level of 6.4% at baseline had sufficiently marked glycaemic alterations to expect improvement in CV outcomes after a 0.3% decrement in HbA1c. In one recent study [39], the risk of macrovascular events was not increased in those with dysglycaemia when HbA1c levels remained inferior to 7%. However, the risk steadily increased by 38% for any 1% increment in HbA1c as soon as HbA1c exceeded the threshold of 7%. This observation adds the body of evidence suggesting that it is difficult to detect any improvement in CV outcomes, whatever the modality of antidiabetic therapy, in those who have near-normal glucose control (HbA1c). Another possible explanation for the lack of any difference between the two arms might be that any small beneficial gain from lowering of ambient hyperglycaemia in the glargine arm might have been counteracted by the potentially deleterious effects of increased glucose variability and, therefore, a greater prevalence of hypoglycaemic episodes, even though most participants remained asymptomatic [40].
Such observations again raise the question of whether earlier implementation of treatments with basal insulin regimens represents (or not) a better option than maintenance with an oral antidiabetic regimen. At this time, the problem remains partly unresolved, although many diabetologists consider that insulin treatment should be initiated at small doses as early as possible in the time course of the disease to both preserve beta-cell function and reduce the risk of long-term diabetic complications [3]. As the results of the ORIGIN trial do not provide any evidence that goes against such a position, they can be said to recommend that healthcare providers implement the use of insulin earlier. However, on the other hand, the study of high-risk individuals with early type 2 diabetes or prediabetes highlights the complexity of the relationships between insulin and macrovascular diseases in such a population. As a consequence, a complete answer to the question of the impact of insulin on atherosclerosis is yet to be found. However, part of the answer may lie in the bimodal effect of insulin. This new concept — that insulin has an antiatherogenic effect at low doses and a proatherogenic effect at higher ones — may help to bridge the controversy over what strategies are to be used in patients with insulin-requiring type 2 diabetes.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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