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Invited commentary

# Insulin therapy in insulin resistance: Could it be part of a lethal pathway?

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Exogenous insulin has been the main stay for the treatment of type I diabetes mellitus (DM) for decades. This successful experience in the treatment of severe, sometimes life-threatening hyperglycemia in type I DM led to the expansion of this use to advanced type II DM patients. In this group of patients, insulin therapy improves metabolic control, and may preserve β-cell function [1,2]. However, insulin treatment may also result in negative effects on other metabolic parameters such as weight gain [3].

Long-term adequate glycemic control in type II DM results in a marked reduction of late DM complications [4]. However, this is driven mainly by a reduction in microvascular complications, such as retinopathy, nephropathy and neuropathy [4], while the reduction of macrovascular complications with more intensive treatment is less well established [5,6]. Few studies have demonstrated a significant reduction in cardiovascular (CV) events and mortality [5,7], whereas contemporary studies found no difference in the rate of CV events and higher mortality rates [6,8].

Nevertheless, attaining similar glucose levels with different drugs may have a diverse effect on other important outcomes, such as CV events, all-cause mortality and rates of hypoglycemia. For example, when compared to sulfonylureas, insulin therapy results in better short-term metabolic control [2], though it results in a higher risk of CV events and all-cause mortality [9]. In contrast, metformin may improve not only metabolic control and weight gain, but it also significantly reduces CV events and mortality when compared with several other classes of anti-diabetics [10]. Taken together this suggest that glucose targets may be imperfect markers of long-term prognosis. While glucose control may be an acceptable target for the prevention of microvascular complications, clinicians may also need to consider other aspects of treatment to improve the prevention of macrovascular complications, such as CV events.

The effects of insulin therapy itself on the prognosis of type II DM has also been in the midst of intensive discussion [11,12]. Several observational studies suggest that insulin therapy may be associated with increased CV events and mortality [13,14] though significant bias cannot be excluded, as patients with more severe DM are also more likely to receive insulin. Nevertheless, others have demonstrated that insulin therapy may be associated with a *reduction* in CV events, despite an increase in incidence of hypoglycemia [7,15].

In the present issue of *Atherosclerosis*, Stoekenbroek *et* al [16] have taken a different approach in order to tease out the controversy of insulin and CV events. The authors performed a nested case–control study of individuals who required insulin after an initial treatment with oral anti-diabetic drugs, using the large cohort of patients included in the Dutch Pharmo database. Due to the particularly large sample size available in this database, the authors were able to match individuals who were hospitalized with a CV event with controls of a similar age, gender, type of oral anti-diabetic drug and duration of DM. Their results suggest that CV events are significantly associated with the use of higher mean insulin dose. The authors further adjusted the results for other metabolic parameters including markers of DM glucose control (Hemoglobin A1c), and the main findings remained essentially unchanged. The authors conclude that in individuals with similar DM control (measured by HbA1c), those who require larger doses of insulin were more likely to develop a CV event during follow up [17]. Albeit a different design, a previous study has also

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demonstrated a significant association of insulin dose and all-cause mortality, though it failed to demonstrate a significant association with CV events [17].

One of the key findings of the present study is that despite similar DM control, the rate of CV events was higher in individuals who received higher insulin doses. Those findings support the idea that glucose control is indeed an imperfect marker for the risk of future macrovascular complications. Since the results remained significant after adjustment for lipid profile, one may infer that not even these biochemical measures are estimators of the increased risk of these individuals.

Another explanation for these findings, as proposed by the authors, is a potential direct effect of insulin therapy leading to a higher risk of CV events. This concept derives from several *in vitro* experiments, though this has not yet translated into unequivocal clinical data. In short, the insulin receptor activates two signaling pathways after insulin binding. The first, phosphatidylinositol 3-kinase (PI3K), is responsible mainly for modulating glucose uptake, while the second, mitogen-activated protein kinase (MAPK), is mainly responsible for the other protein synthesis and cell growth that may lead to intense activation and accelerate the atherosclerotic process [12]. In individuals with insulin resistance, the actual resistance occurs mainly at the PI3K pathway. Thus, although higher insulin is needed to achieve similar glucose reduction effects, the higher insulin dosage may result in more intense effect on the MAPK pathway, leading to an accelerated atherosclerotic process, higher risk of plaque rupture and a more pro-thrombotic state [12].

Interestingly, those two explanations may be complementary. We do not yet have an adequate marker of DM control for the prevention of macrovascular complications, as they cannot be fully understood solely by glucose control. However, the PI3K/MAPK pathway balance, a pathophysiological mechanism related to the degree of insulin resistance, may guide us on where to look for such a marker. One may speculate that two separate, yet correlated targets may compose a more comprehensive disease control for the type II DM in the future. First, glucose control measures, such as fasting glucose and Hba1c, may be the best markers of future *microvascular* complications. Second, a measure of the imbalance between PI3K/MAPK pathways and insulin resistance may be a better marker of future *macrovascular* complications, including CV events.

While insulin therapy may be needed to improve glucose control and prevent microvascular complications, data such as the present study by Stoekenbroek *et* al [16] suggest they may be hazardous for individuals with a high insulin resistance and imbalance between the PI3K and MAPK pathways. Hence, clinicians are urged to consider not only adequate glucose control, but also all potential drug effects, including prevention of micro and macrovascular complications, whenever a new drug is considered for the treatment of a type II DM patient.

## Disclosures

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