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Type 2 Diabetes: Facts and Fallacies Series-II

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In the last editorial "Type 2 Diabetes: Facts and Fallacies" we concluded that the treatment approach for Type 2 diabetes is misdirected, based on the scientific evidence available. Type 2 diabetes presents two key conditions: hyperglycemia and hyperinsulinemia. Existing treatment regimens primarily focus on addressing hyperglycemia while ignoring its underlying cause-insulin resistance. This oversight exacerbates hyperinsulinemia and its associated macrovascular complications. By effectively addressing hyperinsulinemia, we can expect hyperglycemia to diminish as well. Let us see whether any of the ongoing antidiabetic treatment regimens can address hyperinsulenaemia.

Metformin:

Metformin, a commonly used antidiabetic medication, is often labeled as an insulin-sensitizing agent. However, studies using the euglycemic insulin clamp method indicate that it does not improve insulin sensitivity in peripheral tissues, like skeletal muscles, without weight loss.[1-4] Research suggests that metformin primarily functions by reducing hepatic gluconeogenesis rather than addressing peripheral insulin resistance, as it accumulates more in the liver & small intestine than in muscle tissue.[3,5,6] The potential cardiovascular benefits of metformin in type 2 diabetes mellitus (T2DM) patients remain debated. The UKPDS study indicated a 39% relative risk reduction in myocardial infarctions and a 36% reduction in all-cause mortality among metformin users, but these results were based on a small cohort of obese patients with few cardiovascular events, limiting their strength.[7] Conversely, the ADOPT study, which included more participants, found no cardiovascular benefits and reported a trend of increased cardiovascular events among metformin users compared to those on glyburide.[8] A meta-analysis of randomized controlled trials comparing any dose and formulation of metformin with placebo or lifestyle interventions found that metformin was slightly favored across various outcomes, except for stroke; however, none of the endpoints reached statistical significance. In summary, it remains uncertain whether metformin provides any cardiovascular benefits at this time.[9]

Sodium-glucose cotransporter 2 inhibitors (EMPA):

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, particularly empagliflozin, have shown significant cardiovascular benefits in high-risk individuals with type 2 diabetes mellitus (T2DM). The EMPA REG OUTCOME trial[10] demonstrated a 14% reduction in major adverse cardiovascular events (MACEs) and a 35% decrease in heart failure hospitalizations, primarily due to a 38% reduction in cardiovascular mortality. The rapid onset of these benefits suggests that antiatherogenic mechanisms are unlikely to be the primary cause. The CANVAS/CANVAS-R studies corroborated these findings with a 13% decrease in MACEs but highlighted an increased risk of lower-extremity amputations with canagliflozin.[11] The DECLARE study found significant reductions in heart failure hospitalizations & cardiovascular mortality, although MACEs were not significantly reduced.[12] These results align with real-world studies, reinforcing the cardiovascular benefits of SGLT2 inhibitors in reducing MACE and mortality in T2DM patients.

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Glucagon-like peptide-1 receptor agonists and DPP4 inhibitors

Glucagon-like peptide-1 (GLP-1) receptor agonists, including liraglutide and semaglutide, have shown significant cardiovascular (CV) benefits in high-risk populations with type 2 diabetes mellitus (T2DM). The LEADER study reported a 13% reduction in MACEs and a 22% decrease in CV mortality with liraglutide,[13] while the SUSTAIN-6 study demonstrated a 26% reduction in MACE primarily driven by a 39% decline in nonfatal stroke.[14] These studies suggest that GLP-1 receptor agonists improve various CV risk factors, including obesity, hypertension, and dyslipidemia, although the individual improvements are modest and unlikely to fully explain the reduction in MACE. Both liraglutide and semaglutide exert multiple beneficial effects on CV function, including enhancing myocardial function and promoting vasodilation. Recent trials, such as the EXSCEL[15] and REWIND[16] studies, have shown mixed results regarding CV protection, with REWIND confirming a 12% decrease in MACEs with dulaglutide. In contrast, DPP-4 inhibitors, which primarily inhibit glucagon secretion[17,18] and do not have insulin-sensitizing effects,[19,20] have failed to demonstrate any CV protective effect in established cardiovascular disease. Overall, while GLP-1 receptor agonists exhibit promising cardiovascular benefits, the efficacy of DPP-4 inhibitors remains limited in this regard.

Insulin:

Insulin initiates its action by binding to insulin receptors on cell membranes, triggering tyrosine phosphorylation of IRS-1/IRS-2 and activating phosphatidylinositol 3-kinase (PI3K), which enhances glucose transport.[21,22] However, impaired insulin signaling not only disrupts glucose metabolism but also contributes to hypertension and atherogenesis by inhibiting the activation of nitric oxide, a vital vasodilator and antiatherogenic agent.[23,24]

At elevated levels, insulin acts as a potent growth factor[24-26] through the mitogen-activated protein kinase (MAPK) pathway,[27,28] which promotes vascular smooth muscle cell growth and differentiation, activates inflammatory pathways, and can lead to insulin resistance. Despite significant resistance in the IRS-1/PI3K/Akt pathway, the MAPK pathway remains sensitive to insulin and is excessively activated in conditions such as obesity, prediabetes, and early type 2 diabetes.[29-31] Similar insulin signaling defects observed in the skeletal muscle of people with type 2 diabetes and obesity are also found in arterial smooth muscle cells. This results in endothelial dysfunction, characterized by nitric oxide deficiency, which is common in insulin-resistant states, including diabetes and obesity.[32-35] This dysfunction is a key link between insulin resistance and atherosclerotic cardiovascular disease (ASCVD). Additionally, insulin resistance stimulates the production of endothelin-1, which increases vasoconstriction & promotes atherogenesis.[36] It has been proposed that insulin resistance may serve as a protective mechanism for the cardiovascular (CV) system against nutrient overload, particularly in individuals with longstanding diabetes and severe insulin resistance.[37] High-dose insulin therapy in these patients could lead to increased myocardial lipid content, which might overload the electron transport chain, resulting in mitochondrial dysfunction and elevated reactive oxygen species (ROS).[38,39]

Medical therapy generally focuses on addressing single or multiple cardiovascular (CV) risk factors rather than targeting the underlying issue of insulin resistance that contributes to cardiometabolic abnormalities. This approach is highlighted by findings from the National Swedish Registry, which reported a significant decline in CV mortality among individuals with type 2 diabetes mellitus (T2DM) from 1998 to 2014.[40] Despite this improvement, CV mortality rates remained notably higher and plateaued compared to individuals with normal glucose tolerance (NGT).

Thiazolidinediones:

Thiazolidinediones (TZDs) are recognized as the only genuine insulin-sensitizing antidiabetic agents with pioglitazone being the only one widely available globally.[1,41,42] Several large prospective clinical trials and anatomical studies have shown that pioglitazone can reduce cardiovascular (CV) events and promote the regression of atherosclerotic lesions.[42-45] The PROactive study was the first to demonstrate the CV benefits of an antidiabetic agent, showing that in

5,238 patients with type 2 diabetes mellitus (T2DM) who had experienced a prior CV event, treatment with pioglitazone for around 34.5 months resulted in a 16% reduction in the main secondary endpoint of MACEs.[42] However, the primary endpoint, which included MACE along with coronary and leg revascularization, did not achieve statistical significance due to an increase in leg revascularization procedures.

Analysis of double-blind, placebo-controlled studies of pioglitazone indicated a significant reduction in cardiovascular (CV) events among individuals without a prior history of such events (hazard ratio [HR], 0.78; p = 0.005).[46] Supporting these findings, pioglitazone was shown to decrease coronary atherosclerotic plaque volume in the PERISCOPE trial[45] and reduce carotid intima-media thickness (IMT) in the CHICAGO trial.[46] In the IRIS study, 3,876 nondiabetic, insulin-resistant individuals with a recent stroke or transient ischemic attack were treated with pioglitazone or placebo for 4.8 years, resulting in a 24% decrease (HR, 0.76; p = 0.007) in recurrent strokes and CV events, alongside a 24% reduction in HOMA-IR (P<0.0001).[44] A recent real-world study in Finland involving 33,054 T2DM patients treated with pioglitazone & a matched control group found that pioglitazone reduced CV risk by 42% and non-CV risk by 37%. Additionally, a meta-analysis of randomized controlled trials demonstrated that pioglitazone significantly decreased the MACEs endpoint in individuals with insulin resistance, prediabetes, and T2DM.[47] Numerous studies have shown that the insulin-sensitizing antidiabetic medication pioglitazone lowers the risk of atherosclerotic cardiovascular events due to its effects on enhancing insulin sensitivity. The reductions in stroke and myocardial infarction cannot be explained by improved glucose control, since the decrease in HbA1c was relatively small in the PROactive study,[42] and subjects in the IRIS trial were not diabetic.[44]

Type 2 diabetes mellitus (T2M) is a cardiometabolic disease that impacts both microvascular (e.g., retinopathy, nephropathy, neuropathy) and macrovascular (e.g., hypertension, ischemic heart disease, and stroke) systems. Microvascular complications are closely linked to the level and duration of elevated blood glucose, as indicated by HbA1c levels. In contrast, macrovascular complications are only weakly associated with glycemic status and are the leading cause of mortality, accounting for about 75% of deaths due to heart attack and stroke.[6] The failure of intensive glycemic management in studies like ACCORD,[48] ADVANCE,[49] and VADT[50] to significantly lower the rates of heart attacks and strokes implies that hyperglycemia is not a strong risk factor for cardiovascular disease (CVD). Therefore, it can be argued that glucose-lowering treatments may find it challenging to halt the progression or reverse advanced fibrotic, lipid-laden atherosclerotic plaques. Insulin, which was predominantly used in these trials, could have contributed to increased insulin resistance[51,52] & weight gain,[53] both of which are risk factors for atherosclerotic cardiovascular disease (ASCVD).[54] Furthermore, it is now well accepted that the processes leading to accelerated atherosclerosis start long before an established diagnosis of diabetes, that is, in the prediabetic state and among insulin-resistant individuals with normal glucose tolerance.[55-57]

Di Pino and DeFronzo[6] in a review article titled "Insulin Resistance and Atherosclerosis: Implications for Insulin-Sensitizing Agents" concluded that macrovascular complications, such as heart attacks and strokes, are the leading cause of mortality in individuals with insulin resistance syndrome (IRS), as well as in non-diabetic obese individuals, prediabetics, and those with type 2 diabetes mellitus (T2DM). The rise in cardiovascular (CV) mortality in these populations cannot be entirely explained by traditional CV risk factors. Significant evidence indicates that insulin resistance and its underlying molecular causes contribute to the unexplained CV risk. The study concluded that thiazolidinediones are the sole class of genuine insulin-sensitizing antidiabetic medications, with pioglitazone specifically demonstrated to lower cardiovascular events and slow down the atherosclerotic process in patients with type 2 diabetes mellitus (T2DM) who are at high risk. Glucagon-like peptide receptor agonists and SGLT2 inhibitors also reduce

cardiovascular events in these high-risk patients. However, their cardiovascular benefits seem to appear from mechanisms other than minimizing insulin resistance.

Currently, the management of T2DM primarily aims to lower plasma glucose levels rather than addressing the underlying metabolic issues causing hyperglycemia. However, new antidiabetic medications not only reduce glucose levels but also enhance CV risk factors and outcomes in T2DM patients with established cardiovascular disease. Therefore, these medications should be preferred over those that solely lower glucose without benefiting CV risk factors or cardiovascular disease. However, it may not be prudent to broadly endorse the use of pioglitazone for all patients with type 2 diabetes mellitus (T2DM). Lifestyle modifications, particularly those involving regular exercise, provide significant additional health benefits and are cost-effective strategies for improving insulin resistance. Nonetheless, pioglitazone may be appropriate for elderly patients who are significantly debilitated or for individuals with physical limitations, who are unable to engage in adequate exercise. It may also be considered temporarily for patients who, for various reasons, are currently unable to adopt a healthier lifestyle.

Based on the preceding points, insulin resistance seems to be a primary driver of several cardiometabolic risk factors, including type 2 diabetes. Therefore, an effective, durable solution for type 2 diabetes depends on understanding why target cells, especially skeletal muscle cells (where 75-80% of ingested glucose is utilized as energy)[58] become resistant to insulin's action. A key reason for this resistance is that cells are not metabolically active enough to process glucose into energy, often because individuals with diabetes tend to have sedentary lifestyles and consume more energy (calories) than they expend. A sedentary lifestyle and obesity are insulin-resistant conditions linked to impairment of the insulin receptor substrate (IRS) pathway and elevated cardiovascular (CV) mortality.[6] Therefore, both the American Heart Association[59] and the American Diabetes Association[60] advocate for weight reduction and increased physical activity to mitigate CV events and prevent type 2 diabetes mellitus (T2DM) by enhancing insulin sensitivity and maintaining beta-cell function. Indeed insulin resistance is a physiological adaption as a defense mechanism to protect the cells from injury due to excessive nutrient intake. It has been shown that when individuals with diabetes adopt healthier lifestyles, their target cells regain the ability to efficiently convert glucose into energy.[1] With consistent and appropriate lifestyle changes, the majority of patients may even be able to manage their condition without needing insulin injections or oral antidiabetic medications.

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