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WHY SHOULD BE THE STRATEGY OF TYPE 2 DIABETES TREATMENT RADICALLY CHANGED

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Abstract

Insulin resistance is a root cause of Type 2 Diabetes Mellitus (T2DM) appearing long time before the outbreak of hyperglycemia. On molecular level, a complex impairment of various biochemical processes occurs, the most important being the failure of phosphatidylinositol 3-kinase enzymatic chain responsible for activation of glucose transporters and endothelial nitric oxide (NO) synthesis. Therefore, in insulin resistant states the defect of glucose utilization is coupled with NO deficit and vasodilatory impairment, generating a huge body of residual cardiovascular risk. However, majority of drugs administered to treat T2DM (sulfonylureas, high doses of insulin) even amplify this malignant relationship, reflected by aggravated obesity, dyslipidemia and arterial hypertension. Early and tight glycemic control strategy is helpful to prevent cardiovascular complications in younger diabetics and harmful for long lasting diabetes in older patients, dying mostly from macrovascular complications (80%) for which hyperglycemia, responsible primarily for microvascular impairment, is a weak risk factor compared with hypercholesterolemia or high blood pressure. Glucocentric paradigm of T2DM treatment should be therefore revised in favor of pathophysiologic approaches with drugs selected to address multifactorial risk, affecting different components of diabetes pathophysiology, to achieve hypoglycemic goals without worsening obesity, insulin resistance, sympathetic overactivity and NO deficit, for example with dual or triple combinations (with dosage adjusted to glycemia) such as: metformin + SGLT2 inhibitor + GLP-1 agonist or metformin + SGLT2 inhibitor + pyoglitazone. Patients should be strongly advised to enhance physical activity, reduce body weight this being the most effective method to decrease insulin resistance, the key factor of extensive cardiovascular damage.

key words: *sympathetic overactivity, insulin resistance, nitric oxide deficit, cardiovascular risk*

Introduction

According to Taoist philosophy, the way is more important than the goal, the way by itself includes the objectives of our effort. Paraphrasing for Type 2 Diabetes Mellitus (T2DM), it is very important how to reach guideline-established goals of early and optimal glycemic control (HbA1c 6.5-7% DCCT) but simultaneously do not increase insulin

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resistance, linked with severe cardiovascular damage.

T2DM is a chronic systemic cardiometabolic disorder with global vascular impairment which distinctive feature is hyperglycemia. However, hyperglycemia is a major risk factor for diabetes microvascular complications, nephropathy and retinopathy [1-3], opposed to relatively weak impact on macrovascular complications such as myocardial infarction, stroke or peripheral vascular disease [2]. The main macrovascular benefit from improved glycemic control is relatively late-onset beginning 10 years after diabetes treatment [3], pointing therefore on other macrovascular major risk factor such as dyslipidemia, arterial hypertension, obesity, protrombotic states [4,5] and more importantly, insulin resistance as a complex culprit of various factors involved in macrovascular damage.

Insulin resistance, defined as a decreased tissue's sensitivity to insulin, is a root cause of T2DM, appearing long time before the outbreak of main diabetes diagnostic sign – hyperglycemia and even years before impairment of the glucose tolerance. Insulin resistance gradually progress from pre-diabetic condition to the overt T2DM. On molecular level, a complex impairment of various biochemical processes occurs, the most important being the failure of phosphatidylinositol 3-kinase (PI 3-kinase) enzymatic chain responsible for activation of glucose transporters and glucose uptake. As a result of PI 3-kinase defect insulin excessively activates coupled mitogen-activated protein kinase pathway with a series of harmful effects such as: vascular smooth muscle cell proliferation, vasospasms, inflammation and accelerated atherosclerosis. The key point is that PI 3-kinase enzymatic system has a dual function and beside activation of glucose transporters activates a second life important enzymatic structure, endothelial nitric oxide synthase (eNOS) signaling pathway responsible for nitric oxide (NO) synthesis and vasodilation [5].

NO is a highly reactive signaling molecule, a gas which acts as local mediator in various tissues. It acts locally because of its short halftime of degradation (5-10 sec). In vascular tissue NO is the most important vasodilator factor. Endothelial cells permanently produce a little amount of NO in answer to vessel wall blood flow shear stress. NO grants constant tonic vasodilation opposing tonic vasoconstrictor effect generated by sympathetic nervous system. The interplay of these two most potent vasoactive antagonistic factors provides optimal blood flow in accordance with tissues' metabolic demands. Except of vasodilation NO plays a key role in a number of fundamental intracellular events that lead to inhibition of platelet aggregation, endothelial regeneration, suppression of abnormal proliferation of vascular smooth muscle cells and cardiovascular remodeling, affecting almost every aspect of cardiovascular physiology extended to metabolic disorders, insulin resistance and atherosclerosis [6].

The duality of PI 3-kinase cardiometabolic effect (glucose uptake and generation of NO) is not a matter of chance but has a deep intrinsic logic with important clinical consequences. Insulin stimulating PI 3-kinase enzymatic chain exerts vasodilation by endothelial nitric oxide synthase 3 (NOS3) generated - NO production. This dual effect (vasodilatory and metabolic) results in improved blood supply in peripheral tissues, ameliorating intracellular glucose transport and insulin metabolic performance [7]. Therefore, in insulin resistant states the defect of glucose utilization is coupled with endothelial NO deficit and vasodilatory dysfunction. This effect is even worsened by sympathetic

overactivity and accompanied metabolic disorders such as overproduction of triglycerides and free fatty acids leading to vascular lipotoxicity, accelerated atherosclerosis and further vasodilatory impairment.

It is important that insulin resistance-mediated cardiovascular damage occurs long before hyperglycemic manifestation of T2DM and even before impairment of the glucose tolerance. Cardiovascular risk of patients with insulin resistance and metabolic syndrome but without hyperglycemia is comparable to overt diabetes. The meta-analysis of 87 studies performed on 951 083 patients revealed that a relative risk (RR) of cardiovascular disease mortality for patients with insulin resistance and metabolic syndrome but normal glycemia (without diabetes) was RR: 1.75 - RR: 2.40 (insulin resistance - diabetes); myocardial infarction: 1.62 - 1.99; stroke: 1.86 - 2.27 and the risk of all-cause mortality for patients with insulin resistance was 1.32 but only slightly larger, 1.58, for patients with overt T2DM [8].

The negative results of tight glycemic control (HbA1c targeting < 6%) on macrovascular complications in ACCORD, ADVANCE a VADT trials [9,10] was recently backed by persistent increase of cardiovascular death even 9 years after diabetes intensive treatment [11], supported suggestion that hyperglycemia is not a main cardiovascular killer in T2DM. Tight glycemic control is useful primarily for microvascular complications. Every 1% decrement of HbA1c decreases risk of microvascular complications (diabetic retinopathy and nephropathy) by 25-30% [5]. However, the vast majority of patients with T2DM (80%) perish from macrovascular complications (brain and cardiac events) for which hyperglycemia is relatively weak risk factor compared with hyperlipidemia and high blood pressure [5]. The risk of myocardial infarction in diabetics is almost twofold and recurrent infarction is fourfold compared to non-diabetics [12] suggested T2DM to be a macrovascular risk equivalent of myocardial infarction.

The extraordinary complex origin of cardiovascular impairment in T2DM is supported by a large portion of residual cardiovascular risk which still remains after tight glycemic control. It was impossible to prevent 75% of microvascular and 80% macrovascular complications after adjustment of glycemia [2]. This huge residual cardiovascular risk persists in diabetics even after improvement of other large cardiovascular risk factors such as elevated blood pressure and hyperlipidemia [13]. The mathematical analysis of metabolic variables to coronary artery disease in young adults, aged 20 – 30 years, revealed that preventing insulin resistance would avoid 42% of myocardial infarctions. Normalization of systolic blood pressure prevents 36% risk of myocardial infarction, followed by HDL cholesterol with 31%, BMI - 21%, LDL cholesterol - 16%, triglycerides - 10%, fasting hyperglycemia - 9%, smoking - 9% and the family history of cardiovascular disease with 4%. Insulin resistance thus seems to be the most important single cause of myocardial infarction in young individuals [14].

These suggest that except well known, classic cardiovascular risk factors (dyslipidemia, hypertension and hyperglycemia) a mighty underestimated cardiovascular killer may be in play. It is plausible that this cardiovascular damager may be the primary cause of T2DM – insulin resistance coupled with sympathetic overactivity and endothelial NO deficit [15]. This malicious triangle triggers global cardiovascular structural and regulatory impairment including accelerated atherosclerosis and autonomic dysfunction. The coupling of

arterial baroreflex-mediated sympathetic withdrawal with enhanced vessel sensitivity to NO points on interaction between endothelial and autonomic vascular control mechanisms [16] severely jeopardized in diabetes where, in addition to endothelial NO deficit, reduced vascular smooth muscle cell sensitivity to NO-mediated dilation is present [17]. Importantly, the triumvirate of sympathetic overactivity, insulin resistance and NO deficit was also found in hypertensive and ischemic coronary heart disease pointing on a mutual etiopathogenetic background of cardiovascular and diabetic conditions [15,18,19].

Therefore, the main goal of diabetes treatment is to cut of the vicious circle of sympathetic overactivity, insulin resistance and NO deficit. However, in common medical practice majority of drugs administered for diabetes treatment even aggravate this malicious cross-talk relationship. For tight glycemic control is paid by increase in insulin resistance and coupled cardiovascular impairment. This can be seen on patient that gaining weight after receiving antidiabetic treatment. Obesity by itself is a typical carrier of malignant triangle of insulin resistance, worsened NO-dependent vasodilation and sympathetic overactivity [19]. T2DM is only more progressed stage of insulin resistance where impaired glucose tolerance is joined. However, nor sulfanilamide antidiabetics neither insulin are a good choice to treat insulin resistance because their application evokes additional hyperinsulinemia. Extensive clinical evidence suggests that insulin especially in high doses is coupled with body weight gain, insulin resistance and atherosclerosis. Insulin supports lipogenesis and accelerates VLDL synthesis. Insulin in addition is a potent growing factor, stimulates collagen synthesis, vascular smooth muscle cell proliferation and by various genes linked with extensive atherosclerotic impairment [5]. Therefore, hyperinsulinemic drugs (insulin and sulfonylureas) should be applied in second line of diabetes treatment in as low as possible doses, with minimal sufficient increase of serum insulin to control glycemia; and their application is justified because of incapability of other antidiabetics that do not increase serum insulin reduce glycemia sufficiently. Simplified, in T2DM it is necessary to decrease glycemia without weight gain a reliable, visible marker of hyperinsulinemia and insulin resistance. However, everyday clinical practice shows that treat diabetes without weight gain is extremely difficult and needs enhanced patient commitment rather then to rely on pharmacotherapy solely. It is necessary to get rid patients from the illusion that for T2DM treatment drugs are utmost important. The most effective method to decrease insulin resistance and coupled cardiovascular risk is radical change in life stile, regime measures, low carbohydrate and fat diet and bring down the body weight. The increase of physical activity, mainly by aerobic physical training, even without weight loss is effective to decrease insulin resistance [20]. A simple and reliable method how to control effectiveness of insulin resistance treatment is a thorough monitoring reduction of body weight. Accordingly, to prevent cardiovascular events it is necessary to select antidiabetic drugs which have at least neutral or even better, negative effect on body weight and insulin resistance. The oldest drug which seems to fulfill such requirements is metformin.

Suggested most commonly used antidiabetic drugs

Metformin

According to current knowledge, metformin is considered to be the drug of first choice, the cornerstone of T2DM treatment. Metformin is defined as insulin sensitizer because it exerts

hypoglycemic effect without stimulation insulin secretion. The main mechanism of metformin's effect is the decrease of hepatic gluconeogenesis, intestinal glucose reabsorption and the enhancement of glucose uptake by peripheral tissues [21].

Metformin except of its hypoglycemic feature has a favorable effect on lipid profile, fibrinolytic conditions, inflammation and has anorectic property with slight decrease (–0.6 kg) or neutral effect on body weight [22]. Metformin possess a significant cardioprotective effect. From UKPDS trial it follows that early treatment of T2DM with metformin significantly decreased myocardial infarction by 39%, all-cause mortality – 36 % and diabetes-related mortality – 42% compared with control group with conventional treatment [23].

Metformin seems to decrease insulin resistance in various tissues, in liver by suppression of fat accumulation and glycogen synthesis. This is supported by metformin's effectiveness in treatment of nonalcoholic fatty liver disease, a significant marker of insulin resistance in hepatocytes [20]. In skeletal muscles metformin promotes phosphorilation of insulin receptors, activates glucose transporters and glucose uptake. In fatty tissue metformin impedes lipolysis and decreases elevated plasma-free fatty acids, restraining thus the lipotoxic injury associated with worsening of insulin resistance in various tissues including liver, vessels, skeletal muscles and beta pancreatic cells. In endothelial cells metformin decreases insulin resistance reflected by enhanced NO synthesis and vasodilation in peripheral tissues [24-26]. Thus, it seems that metformin's cardioprotective properties are explained by mechanisms independent on glycemic control, mainly by improvement of the insulin resistance and endothelial dysfunction. This is supported by its effectiveness to prevent overt diabetes in patients with impaired glucose tolerance [24] and by attempts to use its cardio-protective properties in patients with cardiovascular conditions but without diabetes [27,28].

SGLT2 inhibitors

A new very promising class of antidiabetic drugs for T2DM treatment is represented by inhibitors of sodium-glucose cotransporter - 2 (SGLT2) in the kidney with favorable effect on cardiovascular mortality. Three main SGLT2 inhibitors (dapagliflozin, canagliflozin and empagliflozin), approved for clinical use by Food and Drug Administration (FDA) and European Medicines Agency (EMA) in USA and Europe, effectively control hyperglycemia inhibiting spatial glucose reabsorption in the kidney.

EMPA-REG OUTCOME was a long lasting clinical study performed on 7 000 patients with T2DM with high cardiovascular risk. The administration of empagliflozin induced a 38% reduction of cardiovascular mortality, 32% reduction of death from any cause and 35% reduction of hospitalization for heart failure. The administration of empagliflozin furthermore had an outstanding nephroprotective effect and significantly impeded worsening of diabetic nephropathy. Because nephroprotective effect was observed during relatively short period of administration, 3.1 years, and the reduction of the HbA1c was not large (−0.28%), it is possible that empagliflozin’s nephroprotective effect was not associated with glycemic control. Most likely the effect was linked with changes in renal hemodynamic, decrement of hyperfiltration and microalbuminuria [1]. Similarly, the reduction of cardiovascular complications can not been explained entirely by not very distinct decrease in HbA1c. Probably inhibition of sympathetic-renin-angiotensin-aldosterone system, the

decrease of body weight, chronic inflammation, plasma uric acid, oxidative stress and the improvement of endothelial dysfunction may participate on cardioprotective effect [1].

Recently finished CANVAS trial revealed that another SGLT2 inhibitor, canagliflozin, reduced cardiovascular events by 14% and renal decline by 40% [29] supporting that class effect of SGLT2 inhibition is in play. A predictive statistical model suggests that also dapagliflozin during 20 years of administration should decrease the risk of myocardial infarction, cardiovascular death and all-cause mortality; but only ongoing DECLARE trial will give definite answer about its cardioprotective properties [1]. However, the risk for lower-limb amputation found to be doubled for canagliflozin in CANVAS should be thoroughly investigated to exclude the class effect for the entire SGLT2 group [29].

Incretin mimetics

A third class of antidiabetic drugs with distinct cardioprotective properties are the incretin mimetics and incretin enhancers. The main mechanism of GLP-1 mimetic hypoglycemic effect lays in stimulation of insulin secretion in blood glucose level dependant manner, suppression of glucagon synthesis, decrease of appetite and slowing down the gastric emptying. LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) study was performed on 9 340 high cardiovascular risk patients. Liraglutide application decreased HbA1c by 0.4%, body weight by 2.3 kg and systolic blood pressure by 1.2 mmHg. Liraglutide was coupled with 13% reduction in risk for cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, compared with those who received placebo [30]; and repeatedly, the reduction of cardiovascular outcomes cannot be explained by decrement in HbA1c rather than by decrease in body weight, blood pressure and coupled insulin resistance.

Dipeptidyl peptidase inhibitors

The next class of drugs with incretin mechanism of action are inhibitors of dipeptidyl peptidase - 4 (DPP-4). Gliptins competitively inhibit DPP-4 and enhance the effect of endogenous incretins (GLP-1 and GIP). However, by DPP-4 inhibition endogenic plasma GLP-1 levels increase but only in physiological range (less then in the case of GLP-1 agonists). The advantage of this class of antidiabetics is in the absence of body weight gain and cardiovascular-neutrality with comparable hypoglycemic effect to sulfonylureas or metformin. Currently the most widely used DPP-4 inhibitors are sitagliptin, saxagliptin, linagliptin and alogliptin. These drugs decrease HbA1c by 0.6% - 0.9%, are safe, well tolerated [22,31] and possess cardiovascular pleiotropic properties [32].

Thiazolidinediones

Thiazolidinedione derivates (rosiglitazone, pioglitazone) are selective antagonists of nuclear peroxisome proliferator-activated receptors (PPARs) which participate in maintenance of energy homeostasis. This class of antidiabetics belongs to insulin sensitizers and enhances glucose transport to fat and muscle cells. Thiazolidinediones ameliorate various components of metabolic syndrome including insulin resistance, dyslipidemia (decrease LDL cholesterol, triglycerides and increase HDL cholesterol), endothelial dysfunction, hypertension and slow down atherosclerosis. Proactive study revealed that pioglitazone significantly decreased composite markers of all cause mortality, nonfatal myocardial infarction and stroke in type 2 diabetics with high cardiovascular risk [33]. Pioglitazone increases

body weight by 2.08 kg compared to placebo plus metformin [22,34] and is contraindicated in patients with heart failure NYHA III-IV class. Furthermore, pioglitazone decreases insulin resistance in liver and therefore is effective in treatment of fatty liver disease [20]. It is important that thiazolidinediones maintain glycemic control for a longer time compared with other class of oral antidiabetics.

Derivates of sulfonylurea

Derivates of the sulfonylurea acts on the level of pancreatic tissue binding on specific β-cells receptors and directly stimulate insulin secretion. Monotherapy with sulfonylureas, especially with first generation compounds (glibenclamide), was coupled with weight gain (2.06 kg) and increase in cardiovascular diseases [22]. From the results of ADVANCE trial, it follows that from sulfonylureas only gliclazide has no significant effect on major cardiovascular events. Furthermore, recent studies showed that gliclazide is the only derivate of sulfonylurea with comparable reduction of cardiovascular outcomes as metformin [9,35]. The neutral cardiovascular effect of gliclazide is probably associated with its high selectivity for pancreatic beta cells, low affinity to myocardial tissue and early hypoglycemic effect depending on actual glycemia. Gliclazide has several further favorable extrapancreatic effects such as antioxidative, antiatherogenic and increases insulin sensitivity [22]. Therefore, this compound should be the drug of choice in treatment of T2DM where for better glycemic control is necessary to raise level of endogenous insulin.

Conclusions

It appears that it is time to revise the priorities of T2DM treatment. Glycemic-centric approach of diabetes management pointed exclusively on tight glycemic control is a historical heritage of type 1 diabetes, which treatment is based on insulin deficit opposed to T2DM grounded on insulin resistance mechanism. The treatment of the hyperglycemia has a potential to deplete microvascular complications with week effect on macrovascular impairment which thanks to eager glycemic control by conventional diabetes therapy tactic may be even worsened. This can occur not only due to acute hypertensive or proarhytmogenic effect of more frequent hypoglycemic episodes, but also thanks to aggravation of diabetes fundamental cardiovascular pathophysiological mechanisms such as obesity, insulin resistance, sympathetic overactivity, and endothelial NO deficit [15,18] leading to deleterious cardiovascular outcomes.

It seems that in usual clinical practice is not taken into consideration enough the well known fact that T2DM is a completely different disease than type 1 diabetes and rigidly standing on the paradigm of maximal reduction of the hyperglycemia. Very often this approach is boosted by deeply anchored public opinion which links diabetes only with hyperglycemia and diabetologists are rated by their capability to cope with only this component of the disease. However aggressive glycemic control tactics may be helpful to prevent cardiovascular complication in younger diabetics and is harmful for older patients with long lasting diabetes on the background of pre-existing cardiovascular conditions. Therefore, diabetes treatment should be strictly individualized, based on patient's age, diabetes duration and on the presence of coexisting macro- and microvascular complications. Optimal treatment of T2DM must encompass reduction of the multifactorial risk, which except of hyperglycemia includes control of the body weight, blood pressure and hyperlipidemia [36], a cluster of factors

interrelated with insulin resistance, the root cause of diabetic cardiovascular impairment.

This approach is in accordance with diabetes pathophysiology, creating larger space to more complexes address macrovascular complication, including at least 80% of residual cardiovascular risk left behind adjustment of hyperglycemia [2]. It is decisive to discuss with patients the change of their life style, decrease of body weight and intensification of physical activity. This is however a challenge for the entire society, not only the task of the healthcare. Patients should be maximally motivated and may be financially rewarded for every 1-kg decrease of their body weight. This aggressive approach should contribute to improvement of general population health status, reducing enormous economic burden of diabetes for society. Treatment of T2DM should be pointed on reduction of insulin resistance, sympathetic overactivity and endothelial NO deficit to maintain stabile and durable reduction in HbA1c. Antidiabetic drugs should be selected to achieve hypoglycemic goals without increase of body weight and coupled insulin resistance, with minimal hypoglycemic episodes and intrinsic cardioprotective property if available. It seems that the entrance therapy of new onset T2DM should be started with combination of various antidiabetics, aimed on simultaneous impact on different components of diabetes pathophysiology, for which in addition was proved decrease of cardiovascular mortality. For example, treatment should begin with dual or triple combination of antidiabetic drugs (with dosage adjusted to glycemia) such as: *metformin + SGLT2 inhibitor + GLP-1 agonist (or iDPP-4)* or *metformin + SGLT2 inhibitor + pyoglitasone*. Of course, such diabetes entrance treatment collides with strong economic limitations. However synergistic cardioprotective effect and favorable cardiovascular outcomes makes such treatment even financially very advantageous.

Drugs that elevate serum insulin (insulin medication or sulfonylureas) should be administrated in as possible lower dosage to avoid worsening obesity, hyperinsulinemia and insulin resistance. From sulfonylureas, this requirement seems to fit gliclazide (for its early onset hypoglycemic effect and neutral cardiovascular outcomes) and from insulins, insulin analogs and especially insulin degludec for its ultralong 42-hour duration of action allowing to reduce dosage of insulin [37], hyperinsulinemia and coupled insulin resistance [5].

It is interesting that a parallel may exist between hypoglycemic and hypotensive treatment of T2DM where the most effective drugs to decrease cardiovascular mortality are hypotensives with favorable effect on sympathetic overactivity and endothelial dysfunction (ACE-inhibitors and AT-1 receptor blockers), which importantly in addition decrease insulin resistance and prevent new onset T2DM [38]. This supports the idea of interconnected etiopathogenetic background and similar therapeutic strategy for treatment diabetes and hypertensive cardiac disease severity of which significantly correlates with preexisting insulin resistance [39]. The decrement of vascular sympathetic activity (achieved pharmacologically or by baroreceptor stimulation technique) has a property to enhance vessel sensitivity to endothelial NO [16], suggested to be a joining point to treat both arterial hypertension and diabetes, allowing to cut off malignant triangle of sympathetic overactivity, endothelial dysfunction and insulin resistance [40], the most important pathogenetic factors for a spectrum of cardiovascular conditions, including T2DM.

And finally, it is important the way how to achieve the goal, early and optimal glycemic control in T2DM, with low as possible dosage of hypoglycemic drugs that worsen obesity, hyperinsulinemia and insulin resistance – the major risk factors of global vascular damage and cardiovascular mortality. Glucocentric paradigm of T2DM treatment should be therefore revised in favor of pathophysiologic approach with combination of antidiabetic drugs with proven intrinsic favorable effect on insulin resistance and cardiovascular mortality.

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