MANAGEMENT OF CARDIOVASCULAR RISK FACTORS IN TYPE 2 DIABETES MELLITUS PATIENTS

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ABSTRACT

People with Type 2 diabetes mellitus (T2DM), compared with non-diabetic individuals, have increased cardiovascular risk. Part of this excess risk is associated with a higher prevalence of other cardiovascular risk factors in these patients, such as obesity, dyslipidaemia, and hypertension. However, the increased cardiovascular risk present in T2DM cannot be attributed entirely to the high prevalence of traditional risk factors and other non-traditional risk factors may also be important for people with T2DM. Evidence suggests that in patients with T2DM, treatment of cardiovascular risk factors is very important in reducing the risk of cardiovascular disease (CVD). The poor control of risk factors observed in the diabetic population supports the need for more aggressive treatment of modifiable cardiovascular risk factors, especially in patients with previous CVD. There is little evidence on the independent association between traditional and non-traditional cardiovascular risk factors, however these risk factors do not appear in isolation and are produced at the same time, exacerbating the risk of a cardiovascular event. Targeting multiple markers of CVD risk offers the best chance of improving CVD outcomes. The objective of this review is to highlight the importance of managing cardiovascular risk factors in patients with T2DM.

Keywords: Type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), cardiovascular risk factors, dyslipidaemia, hypertension, obesity, microalbuminuria, homocysteine, subclinical cardiovascular disease.

INTRODUCTION

Individuals with Type 2 diabetes mellitus (T2DM), compared with non-diabetics have increased cardiovascular morbidity and mortality.[1] Diabetic vascular disease is associated with a 2–4-fold increase in the incidence of coronary heart disease and stroke, and 2–8 times the risk of heart failure.[2] The risk of cardiovascular disease (CVD) follows a gradient and the capture of this gradient depends on the combination of several risk factors.[3] Part of this excess risk is associated with a higher prevalence of risk factors in these patients, such as obesity, dyslipidaemia, and hypertension. Evidence suggests that in patients with T2DM, treatment of cardiovascular risk factors is very important in reducing the risk of CVD.[4,5] The poor control of most of the cardiovascular risk factors observed in the diabetic population[6] supports the need for more aggressive treatment of modifiable cardiovascular risk factors, especially in patients with previous CVD. However, the increased cardiovascular risk present in T2DM cannot be attributed entirely to the high prevalence of traditional risk factors and other non-traditional risk factors may also be important for people with T2DM.[7] Few studies have prospectively demonstrated in T2DM the independent association of non-traditional risk factors with traditional risk factors.[8] In addition, drugs that are currently used in the treatment of T2DM, such as insulin sensitisers and statins, have a variety of different effects on many of these non-traditional risk factors[9,10] which have been discussed extensively in the literature.[11] These risk factors do not appear in isolation but are produced at the same time,[12] exacerbating the risk of a cardiovascular event (Figure 1).

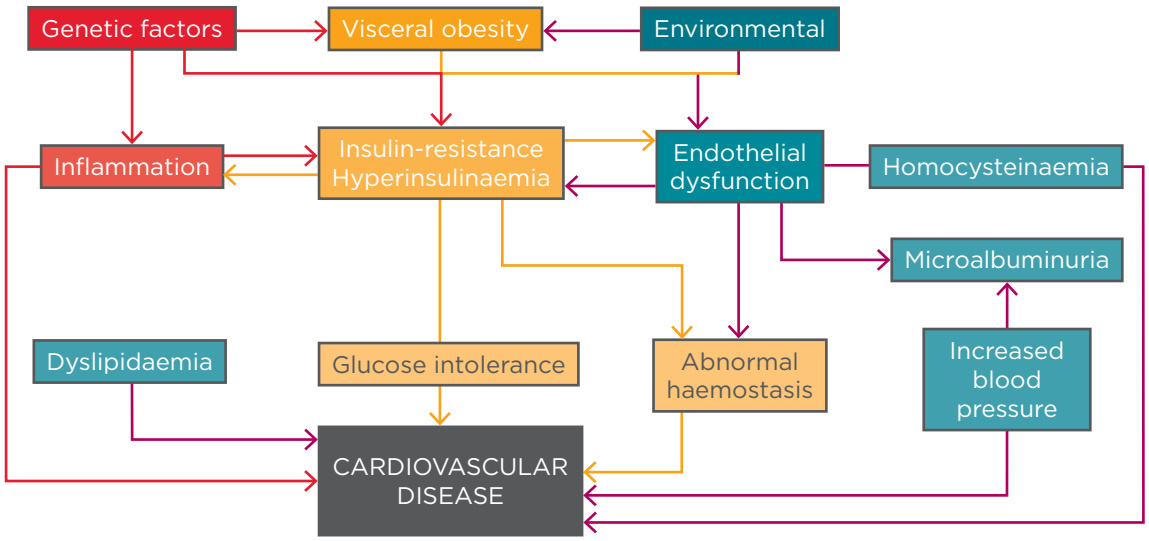

Figure 1: Interactions between traditional and non-traditional risk factors in the onset of cardiovascular disease in Type 2 diabetes mellitus patients.

Table 1: How cardiovascular risk factors affect cardiovascular complications in diabetes.

RISK FACTOR	MECHANISMS
Obesity	• Insulin resistance and defects in insulin secretion • Production of proinflammatory cytokines that causes an inflammatory state contributing to the development of atherosclerotic lesions
Alcohol	• Rise in blood pressure and heart rate without other favourable heart benefits
Hypertension	• Hyperinsulinaemia linked to increased renal reabsorption of sodium, increased sympathetic tone, and increased renin-angiotensin-aldosterone system activity
Cholesterol and lipoproteins	• Atherogenic lipid profile characterised by high triglycerides, low high-density lipoprotein cholesterol, increased apolipoprotein B synthesis, and small dense low-density lipoprotein particles
Smoke	• Elevates circulating free fatty acid levels • Impairs insulin sensitivity, directly or indirectly
Hypoglycaemia	• Rise in heart rate, systolic blood pressure, myocardial contractility, and cardiac output • Exacerbates ischaemia in individuals with occlusive coronary artery disease • Prolongs the QT interval • Deleterious effects on endothelial function, platelet reactivity, and coagulation • Increases inflammatory mediators and blood viscosity
Hyperhomocysteinaemia	• Atherosclerotic role
Microalbuminuria	• Systemic endothelial dysfunction • Glomerular endothelial dysfunction • Damage to glycocalyx, a protein-rich surface layer on the endothelium

The objective of this review is to highlight the importance of managing cardiovascular risk factors in patients with T2DM.

MECHANISMS OF INCREASED RISK

The abnormal metabolic state of diabetes accelerates atherosclerotic disease.[13] A variety of mechanisms can contribute to the increase in coronary heart disease, in addition to the effects on lipid metabolism and blood pressure (BP), with hyperglycaemia as the common trigger (Table 1). It is agreed that there is an increased prevalence of coronary plaques in diabetic hearts, with increased macrophage infiltration, a greater amount of lipid-rich atheroma, a higher incidence of thrombosis, and propensity for rupture.[14]

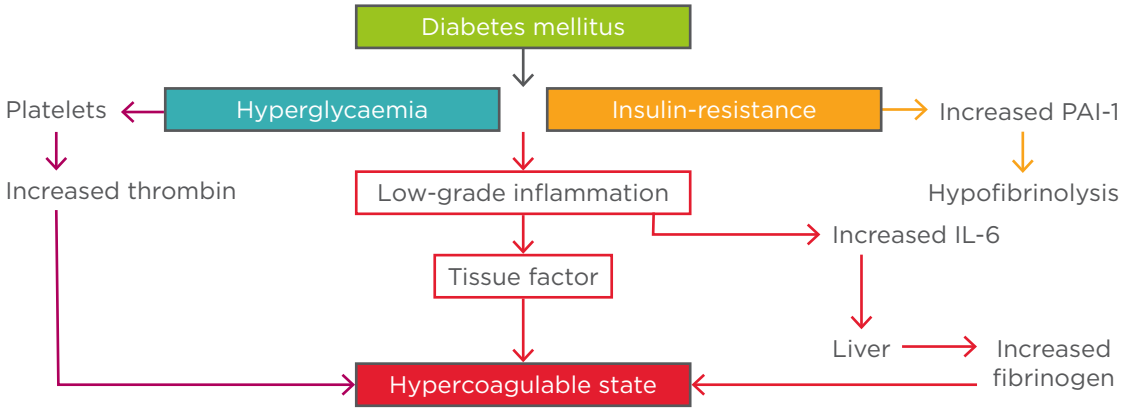

Figure 2: Prothrombotic mechanisms in diabetes mellitus.
IL: interleukin; PAI-1: plasminogen activator inhibitor-1.

The endothelium regulates vascular tone and the interaction of the vessel wall with blood cells and circulating substances.[15] Several mechanisms and biochemical changes cause endothelial dysfunction, including altered glucose metabolism, low grade inflammatory state, impaired insulin signalling, and increased reactive oxidant species generation. The duration of diabetes is related to the degree of impairment.[14] Insulin resistance, in particular, is significantly related to oxidative stress and endothelial dysfunction presents in its early stages. Moreover, hyperglycaemia generates advanced glycation end products that interfere with endothelial cell function and inhibit nitric oxide biosynthesis.[15,16]

Diabetes predisposes patients to abnormalities in pathways involved in coagulation, fibrinolysis, and haemostasis, which increase the risk of thrombus formation (Figure 2). T2DM patients have elevated coagulation factors and impaired fibrinolysis; fibrinogen plasma levels are increased and it is associated with progression of coronary artery calcification. On the other hand, fibrinolytic activity is reduced because circulating tissue-type plasminogen activator activity is decreased as a result of elevated levels of plasminogen activator inhibitor-1; these levels are higher in patients with poorly controlled T2DM.[14,17]

Platelets of diabetic patients have a hyper-reactive phenotype with enhanced adhesion, activation, aggregation, and alpha-granule content release that contribute to accelerated atherosclerosis. The higher adhesion is mediated principally by an increased expression of adhesion molecules and receptors located in the platelet surface, in particular glycoprotein IIb/IIIa and glycoprotein Ib, respectively, which mediate binding to platelet-fibrin and von Willebrand factor interaction. Hyperglycaemia and insulin deficiency and resistance contribute to platelet aggregation and activation by different pathways.[14,18]

TRADITIONAL RISK FACTORS

Obesity

Obesity has been linked to insulin resistance and defects in insulin secretion. Obesity also leads to the production of proinflammatory cytokines that cause an inflammatory state, contributing to the development of atherosclerotic lesions.[19] The primary approach to weight management is a change of lifestyle. A study showed that in the first few years an intensive lifestyle intervention with caloric restriction and increased physical activity produced a weight loss higher than standard intervention with improvements in BP, blood glucose, and lipid profile.[20] When the study was prolonged, it did not find a difference in the rate of cardiovascular events when compared with a standard nutritional intervention.[20] Lifestyle changes can produce a 3–5% rate of weight loss safely. These reductions can be maintained over time and the necessity for medication to control CVD risk factors is reduced.[21]

Different dietary patterns such as the Mediterranean diet, vegetarian, or vegan dietary approaches can be implemented to stop hypertension; low fat and low carbohydrate diets are effective for improving glycaemia and CVD risk factors.[21,22]

In T2DM patients, aerobic and resistance exercise produce noticeable benefits and their effects

are higher in combination compared with each being performed in isolation. Aerobic exercise is recommended for ≥150 minutes per week, ≥3 days per week, and preferably should be increased to 5 days with no more than 2 consecutive days between periods of activity at 40–60% of maximum aerobic capacity. Resistance exercises should be practised 2–3 times per week on non-consecutive days with a moderate intensity including 5–10 exercises during each session with 10–15 repetitions of each exercise.[23]

Bariatric surgery is the most effective treatment for weight loss and improves comorbidities for patients with morbid obesity or a BMI ≥35 kg/m^2 who have multiple conditions and do not respond to standard treatment. These changes have been observed before a significant weight loss, and seem to be consequences of gastrointestinal anatomy restructuring and neuroendocrine mechanisms.[21]

Alcohol

The consumption of a moderate amount of alcohol confers cardiovascular protection[24] and has been associated with a decreased incidence of heart disease in patients with DM and a decreased incidence of DM within a healthy population;[21,25] it is even advised by some associations.[26] However, a meta-analysis of 38 observational studies suggests that previous works overestimate the risk reductions[27] and others show different conclusions, such as a rise in BP and heart rate without other favourable heart effects, or that chronic alcohol consumption, even when it is low or moderate, may trigger the progression or development of T2DM.[28,29]

Hypertension

Hypertensive diabetic patients are at increased risk of morbidity and cardiovascular mortality. In these patients, elevated BP often occurs before the onset of a moderate increase in albuminuria. In the pathophysiology of hypertension in diabetics the development of diabetic nephropathy is involved, there is expansion of extracellular fluid volume, and increased arterial stiffness.[30] Hypertension is related to hyperinsulinaemia linked to increased renal reabsorption of sodium, increased sympathetic tone, and increased renin-angiotensin-aldosterone system activity.[31]

It is important to control BP levels at an early stage.[32] According to the recommendations of the American Diabetes Association (ADA) 2016,[33] patients with BP >120/80 mmHg should be advised on lifestyle changes such as weight loss, reduced fat diet, exercise, salt restriction, and not smoking or drinking alcohol excessively. Patients with BP ≥140/90 mmHg should start antihypertensive medications. The target BP for most people with DM is <140/90 mmHg. Achieving a lower systolic BP (e.g. <130 mmHg) may be appropriate for younger patients who do not require multiple drugs to achieve it.[34,35] In people aged 40–70 years, for every 20 mmHg increase in systolic BP or 10 mmHg increase in diastolic BP, CVD risk doubles (BP values ranging from 115/75–185/115 mmHg).[30] In clinical trials, antihypertensive therapy has been associated with a 35–40% reduction in the incidence of stroke, a reduction of 20–25% in the incidence of myocardial infarction, and a reduction of >50% in heart failure.[36]

Antihypertensive drugs of choice in diabetics are angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers. These drugs have no substantial toxicity or side effects, except for cough and raising the plasma potassium concentration in patients with underlying hyperkalaemia or renal insufficiency. Also, they may lower the plasma glucose concentration by increasing responsiveness to insulin[37] and have no effect on lipid metabolism. They protect against the progression of moderately increased albuminuria and severely increased albuminuria due to T1 and T2DM and have been evaluated for primary prevention of diabetic nephropathy.[38,39] They may also slow the progression of retinopathy.[40]

Angiotensin II receptor blockers seem to have the same benefits as ACE inhibitors in terms of renal protection in patients with nephropathy due to T2DM.[38,39] The LIFE trial in which the efficacy of these drugs was compared with a beta blocker reported a significant reduction in cardiovascular morbidity and mortality with losartan in a subset of high-risk patients.[41] The combination therapy of an ACE inhibitor and angiotensin II receptor blocker is not recommended as it has been observed that most benefits are not achieved and side effects increase compared with monotherapy.[42]

Thiazide diuretics at low doses (for example 12.5mg or 25mg per day of hydrochlorothiazide) are a good antihypertensive treatment for diabetics, especially in combination with ACE inhibitors and angiotensin II receptor blockers. The combination reduces diuretic-induced hypokalaemia, hyperlipidaemia, and hyperuricaemia.[43] Beta

blockers are an effective treatment for hypertension in diabetic patients, but are not recommended due to the modest worsening of glycaemic control seen with metoprolol and other beta blockers that also has been associated in non-diabetic patients with a higher incidence of new-onset diabetes.[44] Calcium channel blockers are a treatment option for hypertension in diabetics in combination therapy with ACE inhibitors or angiotensin II receptor blockers.[42] Alpha blockers are not a first-line therapy for hypertension in these patients due to their adverse effects, such as orthostatic hypotension, but would be an option for combination therapy in older male patients with prostatism.

Cholesterol and Lipoproteins

In T2DM, dyslipidaemia is characterised by a atherogenic lipid profile with high triglycerides, low high-density lipoprotein cholesterol (HDL-C), increased apolipoprotein B synthesis, and small dense low-density lipoprotein (LDL) particles.[45] This LDL subtype plays an important role in atherogenesis. Clinical trials widely demonstrate that lowering LDL-C with drugs reduces the risk of major coronary events regardless of diabetes status.[46]

Recommendations for lipid management in Type 2 diabetes mellitus

T2DM patients must reduce their intake of cholesterol, saturated, and trans-fat, and increase omega-3 fatty acids, viscous fibre, stanols/sterols intake, weight loss, and physical activity.

Low-density lipoprotein cholesterol

Elevated LDL-C is identified as the primary target of lipid-lowering therapy by both the American Heart Association (AHA) and the ADA. The new American College of Cardiology (ACC)/AHA cholesterol guidelines indicate that all patients with DM between the age of 40–75 years and with LDL-C levels between 70–189 mg/dL should be treated with a moderate-intensity statin (ACC/AHA Class I; ADA Level of Evidence A). Patients with DM between 40–75 years of age and with a ≥7.5% estimated risk of CVD, should be treated with statin therapy of high intensity (ACC/AHA Class IIa; ADA Level of Evidence B). Among individuals with DM who are <40 or >75 years of age, practitioners should evaluate the benefit of statin treatment (ACC/AHA Class IIa; ADA Level of Evidence C).[47] Since 2015, the ADA practice guidelines are concordant with the AHA guidelines.[33]

Triglycerides

Triglyceride-rich lipoproteins represent a secondary target of lipid-lowering therapy. The 2013 ACC/AHA guidelines on the treatment of cholesterol provide no evidence-based recommendations for the evaluation or treatment of hypertriglyceridaemia to reduce CVD risk.[47] In accordance with the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) Guidelines, the panel continue to recommend the evaluation of secondary causes and the treatment of patients with fasting triglycerides >500 mg/dL to prevent more severe hypertriglyceridaemia and pancreatitis. ADA clinical practice guidelines 2016 indicate that combination therapy (statin/fibrate and statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone and is not generally recommended.[33] However, therapy with statin and fenofibrate may be considered for men with both triglyceride level ≥204 mg/dL (2.3 mmol/L) and HDL-C level ≤34 mg/dL (0.9 mmol/L).[33]

High-density lipoprotein cholesterol

HDL-C is not a target for therapy according to the ACC/AHA cholesterol treatment guidelines.[47] However, the ADA recognise desirable levels of HDL-C are >40 mg/dL in men and >50 mg/dL in women.[33]

Sex

It is known that some of the most common acute coronary syndromes in women are myocardial infarction associated with non-obstructive coronary artery, spontaneous dissection of the coronary artery, and stress-induced cardiomyopathy syndrome (Takotsubo syndrome). Women are also more likely to present with heart failure with preserved ejection fraction, and peripheral arterial disease.[48]

Smoke

Smoking acutely elevates circulating free fatty acid levels,[49] a negative factor for insulin-mediated glucose uptake. It is possible that nicotine impairs insulin sensitivity via this mechanism, directly or indirectly. The Framingham Study[50] showed that smokers have an increased risk of myocardial infarction or sudden death. In addition, there was a relationship between risk and the number of

cigarettes smoked per day, while former smokers had a morbidity and mortality from coronary heart disease similar to that of individuals who had never smoked.[50]

NON-TRADITIONAL RISK FACTORS

Hypoglycaemia

Hypoglycaemia is a well-recognised side effect of glucose lowering therapies and a major factor limiting glucose control in diabetic patients, particularly in those with long-standing disease.[51] There are several mechanisms by which hypoglycaemia may promote adverse cardiovascular outcomes.[52-54] Contra-regulatory hormones release and autonomic neural activation occurs when glucose falls below 70 mg/dL; these changes include a rise in heart rate, systolic BP, myocardial contractility, and cardiac output. These effects may exacerbate ischaemia in individuals with occlusive coronary artery disease. Hypoglycaemia also prolongs the QT interval and has deleterious effects on endothelial function, platelet reactivity, and coagulation, and increases inflammatory mediators and blood viscosity. Patients treated with insulin or insulin secretagogues should be asked regularly about the occurrence of hypoglycaemia, and therapy should be adjusted.

Hyperhomocysteinaemia

The close relationship between hyperhomocysteinaemia and CVD confirms the atherosclerotic role in the same.[55] Homocysteine may be elevated in blood enzyme genetic defects, nutritional deficits of vitamin cofactors, renal failure, smoking, etc. Hyperhomocysteinaemia is an independent cardiovascular risk factor. To reduce the concentration of homocysteine it is necessary to treat patients with folic acid, vitamin B6, and vitamin B12. In one study the levels normalised within 2–6 weeks.[56]

Microalbuminuria

The epidemiology of microalbuminuria reveals a close association with systemic and glomerular endothelial dysfunction and in particular, damage to glycocalyx, a protein-rich surface layer on the endothelium.[57] Microalbuminuria is a marker for diabetic nephropathy and an early marker of vascular damage.[58] Determination of microalbuminuria has been shown to be useful to identify patients with T2DM at a high risk of renal disease and CVD development.[59] Microalbuminuria is associated with higher cardiovascular mortality, especially in diabetics, but the direct association between microalbuminuria and vascular wall properties is still not clear.[60] The treatment of choice is antihypertensive angiotensin inhibitors, although administration of aspirin and a statin should be considered for diabetic patients.

ASPIRIN THERAPY

Currently the potential to use aspirin for the primary prevention of CVD events in diabetic patients remains controversial. In secondary prevention, aspirin reduces CVD events[61] and in the general population, aspirin is effective in preventing non-fatal myocardial infarction in men; for women, the evidence is less clear but aspirin appears to reduce the risk of stroke.[62]

Current Clinical Guidelines for Aspirin Administration in Primary Prevention Recommendations[33,63]

Low-dose aspirin (75–162 mg/day) is recommended for patients with a 10-year CVD risk of ≥10% and without an increased risk of bleeding (ACC/AHA Class IIa; Level of Evidence B) (ADA Level of Evidence C). This includes most men or women with diabetes aged ≥50 years who have at least one additional major risk factor (family history of premature atherosclerotic CVD, hypertension, smoking, dyslipidaemia, or albuminuria). Low-dose aspirin is reasonable in adults with DM at intermediate risk (10-year CVD risk, 5–10%) (ACC/AHA Class IIb; Level of Evidence C) (ADA Level of Evidence E). Aspirin should not be recommended for atherosclerotic CVD prevention for adults with diabetes at low atherosclerotic CVD risk (10-year atherosclerotic CVD risk <5%), such as in men or women with diabetes aged <50 years with no major additional atherosclerotic CVD risk factors, as the potential adverse effects from bleeding likely offset the potential benefits. (ADA Level of Evidence C).

SUBCLINICAL CARDIOVASCULAR DISEASE ASSESSMENT

It has been difficult to demonstrate that detecting CVD in its preclinical or subclinical state will reduce event incidence or enhance overall patient outcomes, especially in an era when aggressive CVD risk factor reductions are widely endorsed for this population.[21]

Screening Tests for Asymptomatic Cardiovascular Disease in Diabetic Patients

Electrocardiogram

Electrocardiograms (ECGs) may detect evidence of prior myocardial injury or ischaemia. In cohort studies, pathological Q waves, left ventricular hypertrophy (particularly if accompanied by repolarisation abnormalities), QRS prolongation, ST-segment depressions, and pathological T-wave inversions are associated with increased risk of CVD events. Data from the UK Prospective Diabetes Study (UKPDS) demonstrate that an abnormal ECG is an independent risk factor for all-cause mortality and fatal myocardial infarction in diabetic patients. Nowadays, ECG is not recommended by the ADA, however the AHA says that it is reasonable to obtain a resting ECG in asymptomatic adults with diabetes.[64-66]

Other screening tests

Other screening tests are exercise or pharmacological myocardial perfusion imaging (nuclear scintigraphy), exercise or pharmacological stress echocardiography, ankle-brachial index, and coronary artery calcium scoring by electron-beam computed tomography.[21] Nowadays further large and randomised trials are needed to determine whether screening for subclinical CVD can reduce CVD event rates in diabetic patients.[21]

CONCLUSIONS AND FUTURE DIRECTIONS

There is consistent evidence that optimal glycaemic control, along with control of cardiovascular risk factors, is necessary for reducing CVD in T2DM patients. Targeting multiple markers of CVD risk hopefully offers the best chance of improving CVD outcomes. There have been advances in our understanding of the role of non-traditional risk factors for CVD in T2DM. This understanding should gradually lead to development of more effective therapeutic strategies to prevent cardiovascular events. Research efforts need to focus on the factors that make islets susceptible to dysfunction and failure, particularly those that are acquired in early life, as these may be preventable. Epigenetic regulation of metabolic genes may be one of these fields.

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