

Diabetes in the Era of the Hapo Study



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Noncommunicable diseases (NCDs) are the cause of almost 63% of deaths worldwide. More than 90% of these deaths occur in low and middle-income countries and could have been prevented. The 66th World Health Assembly endorsed the WHO Global Action Plan for prevention and control of NCDs (2013-2020) focusing on cardiovascular diseases, cancer, chronic pulmonary diseases and diabetes which make the largest contribution to overall death rate having also a huge economic and social cost. The Global Plan recognizes that conditions in which people live and work and their lifestyles influence their health and quality of life.¹

Obesity is one of the major risk factors for cardiovascular disease and diabetes and represents a global epidemic causing 2, 8 million of deaths each year. Risks of coronary heart disease (CHD), stroke and type 2 Diabetes increase proportionally with Body mass index (BMI), but it also increases the risk of cancer of the breast, endometrium, colon, kidney and gall bladder.

Type 2 diabetes results from the body's ineffective use of insulin and its largely the result of excess body weight and physical inactivity. Adults with diabetes have a 2-3 fold increased risk of heart attacks and strokes and it is also the leading cause of kidney failure. The fact that 80-90% of patients with overweight with abdominal fat distribution are type 2 diabetics and that strategies based in weight loss have demonstrated to reduce diabetes complications, led to define a new concept: "diabetesity".² This new term reflects clearly the relationship between overweight and obesity as the necessary causes of type 2 diabetes and hence the need to understand pathophysiology of overweight to prevent diabetes and its complications.

It is well known that high prevalence of obesity in our societies is strongly linked to sedentary lifestyle and high-fat diets. But these factors don't have the same effects in all individuals as there must be some

genetic predisposition. The theory of fetal programming of diseases was first suggested by Barker in 1989 when he reported the relationship between birthweight and ischemic heart disease and impaired glucose control.^{3,4} Since then, many evidence has been published in favor of prenatal origins of adult diseases.

Environmental factors acting during pregnancy have a large-term effect in the offspring's adult life. It has been described that newborns from diabetic mothers had greater risks of overweight and diabetes than their siblings born before the same mother developed diabetes.⁵ To determine the role of the intrauterine diabetic environment per se, the prevalence of diabetes and the mean BMI was compared in siblings born before and after their mother was recognized as having diabetes. Nuclear families in which at least one sibling was born before and one after the mother was diagnosed with type 2 diabetes were selected. BMI of men whose mothers had diabetes mellitus during their pregnancy was greater than in their brothers born before their mother was diagnosed with diabetes. Furthermore, this epigenetic influence can affect not only to first generation but also to grandchildren as it was described in the Dutch Hunger cohort where offspring from mothers who were pregnant during a severe famine developed increased adiposity and transmitted this phenotype to their progeny.⁷

Animal models have shown that both paternal and maternal metabolic history can produce epigenetic changes in offspring through different patterns of methylation of DNA, chromatin remodeling and noncoding RNA that promote gene silencing.⁸

Epigenetic changes contribute to modulate phenotype through adipose tissue programming. Adipose tissue is an active endocrine organ^{9,10} that regulates lipid synthesis, modulates insulin sensitivity but also intervenes in inflammatory response via the production of soluble factors known as adipocytokines.

kines (*metaflammation*).^{11,12} In obesity, this proinflammatory state provokes an imbalance between adipokines that cause insulin resistance (TNF-alpha and leptin) and those promoting insulin sensitivity like adiponectin.¹³ Hyperinsulinemia resulting from insulin resistance increases lipogenesis, hepatic production of very low density lipoprotein (VLDL) and hypertriglyceridaemia.¹⁴

Gestational diabetes mellitus (GDM), a state of insulin resistance during pregnancy, is estimated to occur in one of every six pregnancies.¹⁵ As with maternal obesity, this condition is in rise and the age of onset of diabetes is declining. GDM is associated with large weight at birth, shoulder dystocia, increased cesarean section rates, preeclampsia and subsequent development of type 2 diabetes. But the most important sequelae for the fetus result from long exposure to hyperglycemia and altered metabolic environment causing epigenetic changes leading to increased risk of obesity, diabetes and dyslipidemia in adult life.

Despite the great impact that gestational diabetes has on perpetuation of global diabetes problem, in most of the countries diagnosis and management has not correctly been established. Different strategies are used worldwide such as testing only risk patients, scoring systems or universal two-stepped or one step approaches, every of them based on different algorithms and cut-off values.

In 2010 The International Association of Diabetes in Pregnancy Study Groups (IADPSG), after carrying out a huge international multicentric study involving 25000 patients known as the HAPO (The Hyperglycemia and Adverse Pregnancy Outcomes) study, proposed consensus cut-off values for fasting, 1 hour and 2 hour 75-OGTT, defining GDM based on odds ratio of 1.75 compared with the mean. HAPO remarked the idea of hyperglycemia as a continuous variable directly associated with adverse maternal and perinatal events. Diagnosis of GDM proposed by IADPSG is therefore more easy (one step approach) and efficient as it puts the focus on adverse events (large weight at birth, cesarean section, fetal insulin levels and neonatal fat content).

The HAPO criteria have been adopted by the WHO and the American Diabetes Association (ADA). The International Federation of Gynecology and Obstetrics (FIGO) has created a Working Group on Hyperglycemia in Pregnancy to implement evidence-based guidelines and develop projects of research and training on diagnosis and management of GDM. FIGO recommends that international attention should be focused on the link between maternal health and NCDs on the sustainable developmental goals agenda. All pregnant women should be tested using a one-step procedure following the IADPSG criteria for diagnosis of GDM. FIGO also insists that women with GDM should receive practical education on nutrition and physical exercise. If lifestyle changes are not sufficient to achieve an optimal control, then some drugs like metformin, glyburide or insulin should be considered as a safe and effective treatment. In the postpartum period a regular follow-up should be established in order to reduce maternal and child risks.

In conclusion, diabetes is a global epidemic that threatens quality of life of a growing number of people from all over the world. Epigenetic changes transmit metabolic disorders from actual to next generations, increasing seriously their risks of cardiovascular disease and diabetes. More research is needed to fully understand the link between intrauterine environment and changes in adult phenotype. Governments, institutions and health providers should launch efficient projects to raise awareness about the risks of diabetes. It's imperative to implement IADPSG recommendations and to focus on giving women adequate recommendations on nutrition and physical activity in order to reduce the impact of GDM on noncommunicable diseases.

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