La Medicina del Lavoro

Med Lav 2019; 110, Suppl 2: 5-9
DOI: 10.23749/mdl.v110i2-S.9741

Diabetes mellitus: up-to-date on antidiabetic drugs and hypoglycemic risk for the occupational physician

Emanuela Orsi, Veronica Resi
UO Endocrinologia e Diabetologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

Keywords: Diabetes mellitus; hypoglycaemia; chronic complications; treatment

Parole chiave: Diabete mellito; ipoglicemia; complicanze croniche; trattamento

Summary
Diabetes Mellitus (DM) is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. Diabetes and hyperglycemia cause chronic complications: cardiovascular disease, blindness, kidney failure and lower-limb amputation, that can lead to the exclusion of some work tasks. Diabetes drugs, as insulin or sulphonylureas, can cause hypoglycemia and the worker may be at risk of accidents. In recent years, numerous innovative drugs have become available and it is very important that the occupational physician knows their mechanism of action and their side effects since they could influence the worker's job. Finally, the occupational physician could play a role in the prevention of type 2 diabetes: this is why it is important to know the disease, how to diagnose it and how to change the lifestyle in workers at risk.

Riassunto
«Diabete mellito: aggiornamento su farmaci antidiabete e rischio ipoglicemico per il Medico del lavoro». *Il diabete mellito (DM) è una malattia cronica complessa che richiede cure mediche continue con strategie multifattoriali, per ottenere una riduzione del rischio di complicanze, oltre al controllo glicemico. Il diabete e l'iperglicemia causano complicazioni croniche: malattie cardiovascolari, cecità, insufficienza renale e amputazione degli arti inferiori, che possono portare all'esclusione da alcune attività lavorative. I farmaci per il diabete, come l'insulina o le sulfoniluree, possono causare ipoglicemia e mettere a rischio di incidenti il lavoratore. Negli ultimi anni si sono resi disponibili farmaci innovativi per la cura del diabete ed è molto importante che il medico del lavoro conosca il loro meccanismo d'azione e i loro effetti collaterali, poiché potrebbero influenzare l'attività lavorativa. Infine, il medico del lavoro potrebbe svolgere un ruolo nella prevenzione del diabete di tipo 2: ecco perché è importante conoscere la malattia, come diagnosticarla e le strategie per cambiare lo stile di vita dei lavoratori a rischio.*

Corresponding author: Emanuela Orsi, UO Endocrinologia e Diabetologia - Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico. - E-mail: emanuela_orsi@yahoo.it

Epidemiology

Recent data estimated that 438 million people aged between 20-64 years will suffer from DM by the year 2045 (4). Type 1 Diabetes Mellitus (T1DM) is more prevalent in children, especially those who range from birth to 14 years old, but individuals of any age can be diagnosed with it, with an excess of male seen among young adults. On the other hand, adults or obese individuals are mostly affected by Type 2 Diabetes Mellitus (T2DM), but it can occur in children too according to recent reports. Also, T2DM is the most common type of diabetes, accounting for around 90% of all cases of diabetes. Globally, the prevalence of T2DM is high and is rising across all world regions. This rise is due to the aging of population, economic development and increasing urbanization leading to more sedentary lifestyles and greater consumption of unhealthy foods linked with obesity. Patients with T2DM have a higher risk of death from cardiovascular causes compared with their nondiabetic counterparts, and the mortality rate of DM-associated cardiovascular disease varies among different ethnic and sex groups (8). In 1984 the American Diabetes Association adopted the following position on employment "Any person with diabetes whether insulin or non-insulin treated should be eligible for any employment for which he/she is otherwise qualified (1). Previous research has found that people who left the labor force early due to diabetes had an income five times lower than those who did not have a chronic illness (13). Men and women with T2DM were 7.1% and 4.4%, respectively, less likely to be working compared to their non-diabetic counterparts (15). The same study also found that people with diabetes had more work-loss days per year than those without the disease.

Physiopathology

DM is a metabolic disease commonly characterized by an increase of the blood glucose levels that warrant frequent monitoring and proper control. Pancreatic beta cells produce the hormone insulin which facilitates the absorption of glucose into the cells in order to provide energy and is also involved in a variety of other functions. T1DM is typically associated with failure in insulin production resulting from the destruction of pancreatic β-cells by T-cell-mediated autoimmunity. T2DM occurs due to lack of insulin production and insulin sensitivity. It is mainly classified into many types, however the most common is T2 DM. A few susceptible genes were identified to be risk factors for T1DM. These include some of the human leukocyte antigen (HLA) types. Studies shows that identical twins have a higher likelihood to develop T1DM than fraternal twins, showing a strong familial genetic predisposition. T1DM can also be triggered by environmental factors such as viral infections, low levels of vitamin D and several dietary and lifestyle factors such as childhood obesity, rapid growth in infancy, older maternal age and short duration of breastfeeding. In summary, the onset of T1DM appears to be related with a complex interplay of genetic, immune and environmental factors that destruct the pancreatic β-cell function. Insulin resistance is the most powerful predictor of future development of T2DM and cardiovascular disease (CVD) and represents a therapeutic target once hyperglycemia is present (14). Insulin resistance is responsible for the physio-pathologic process where cells fail to respond normally to insulin. Liver, skeletal muscle and adipocytes are mainly involved. Dysregulation of fatty acid metabolism plays a pivotal role in the pathogenesis of insulin resistance in skeletal muscle, with decreasing insulin-stimulated glucose uptake due to impaired insulin signaling and multiple post-receptor intracellular defects including impaired glucose transport and glucose phosphorylation, and reduced glucose oxidation and glycogen synthesis (3).

Suppression of glucose production in the liver is decreased and activation of GLUT-4-mediated glucose uptake does not take place, particularly in skeletal muscles and adipocytes. This overall failure typically is not due to low insulin levels. Instead, insulin-stimulated signal transduction pathways for peripheral glucose uptake and for hepatic glucose production are reduced, including insulin receptors and downstream mediators. Hyperglycemia is then driven by excessive hepatic glucose production and reduced uptake of glucose by peripheral tissues (3). To counteract glycemic elevations, β cells of the

pancreas boost insulin production, further contributing to hyperinsulinemia. The risk factors for T2DM are a sedentary lifestyle, an incorrect diet that involves the consumption of foods rich in carbohydrates, fats, and sugary drinks but low in fiber and which can also be linked to genetics. Obesity and a previous gestational diabetes are also correlated with incidence of T2DM (1, 2)

Classification and diagnostic criteria

Diabetes can be classified into the following general categories:

1. T1DM, due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency
2. T2DM, due to a progressive loss of –β cell insulin secretion frequently on the background of insulin resistance
3. Gestational diabetes mellitus (GDM), diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes, such as neonatal diabetes and maturity-onset diabetes of the young (MODY), diseases of the exocrine pancreas, such as cystic fibrosis and pancreatitis, and drug- or chemical-induced diabetes, such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation (1). In Table 1 Pre-diabetes and Diabetes diagnostic criteria are described (1). The onset of T2DM is usually slow and its usual presentation without the acute metabolic disturbance seen in T1DM means that the exact time of onset is difficult to determine. As a result, there is often a long pre-detection period and as many as one-third to one-half of T2DM cases in the population may be undiagnosed because they may remain without symptoms for many years. When unrecognized for a prolonged time period, the complications of chronic hyperglycemia may develop.

Glycemic target and hypoglycaemia

Table 2 describes glycemic targets for a good metabolic control in diabetic patients, according to national and international Scientific Societies. It is important to underline that these goals must be achieved without hypoglycemia. Hypoglycemia is the most important predictor of cardiovascular mortality, as shown in large studies on diabetics at

Table 1 - Pre-diabetes and Diabetes mellitus diagnostic criteria

Impaired fasting glucose (Ifg)	Impaired glucose Torelance (igt)	Diabetes
Fasting plasma glucose 6.1-6.9 mmol/L (110 to 125 mg/ dL) and Two-hour plasma glucose <7.8mmol/L (140mg/dL) following a 75g oral glucose load	Fasting plasma glucose <7.0 mmol/L (126 mg/dL) and Two-hour plasma glucose ≥7.8 <11.1mmol/L (≥140 to <200 mg/dL) following a 75g oral glucose load	Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) or Two-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) following a 75g oral glucose load or A random glucose > 11.1 mmol/L (200 mg/ dL) or HbA1c ≥ 48 mmol/mol (equivalent to 6.5%)

Table 2 - Glycaemic target

	ADA	IDF	ACE/AACE	Consensus (SID)
HbA_{1c} (%)	<7,0	< 6,5	< 6,5	<7 (<6.5)
Fasting glucose/preprandial glycemia (mg/dl)	90–130	<110	<110	70-130
Postprandial glycemia (mg/dl)	<180 (peak)	<145 (1–2 hrs)	<140	<180 (<140)

risk or already with cardiovascular disease (7). Insulin therapy can cause hypoglycemia, and it is essential to titrate the dosage based on the characteristics of the patient, such as age, diabetes duration, life expectancy, etc. The possible consequences of hypoglycemia are described in Fig. 1. New drugs for T2DM are now available that do not cause hypoglycemia and can achieve glucose values as in non-diabetic people. For diabetic workers this aspect is very important, especially for those employed in shift work, at night or for special tasks, due to the risk of accidents and worsening of glycometabolic control.

Treatment

Due to destruction of pancreatic β-cells by T-cell-mediated autoimmunity, insulin therapy is the only choice in the treatment of T1DM. The main objective is to reproduce the physiological kinetics of the hormone, without hypoglycemia. Insulin preparations now available are shown in Table 3.

The cornerstone of T2DM treatment is a healthy lifestyle which includes the adoption of a healthy diet, increased physical activity, smoking cessation plan and maintenance of a healthy body weight. If attempts to change lifestyle are not adequate to control blood glucose levels, oral medication is usually initiated for treatment of hyperglycemia with metformin being the most commonly used initial treatment worldwide. Recent studies have shown that in patients with type 2 diabetes and an elevated risk of cardiovascular and kidney disease, the rate of cardiovascular events and kidney failure was lower among patients receiving SGLT2 inhibitors and GLP1 RA than in the placebo group (12, 11, 9, 17, 16). These consistent results have contributed to modify the algorithm of treatment in T2DM in recent Guidelines (5). So, if glycometabolic control with metformin is not adequate, a range of combination therapy options are now available, including thiazolidinediones (TZD), Dipeptidyl Peptidase 4 inhibitors (DPP-4 i), Sodium-glucose transporter 2 inhibitors (SGLT2 i), Glucagon Like Peptide-1 receptor agonists (GLP1 RA), according to the risk of chronic complications. Combination therapy is started for faster, more effective control on blood glucose and dose reductions in individual medications. When oral hypoglycemic medications are unable to control hyperglycemia to recommended targets, insulin injections may be prescribed. Exogenous insulin can be combined with various oral antidiabetic drugs or GLP-1RA to allow insulin dosage lowering and reduction in weight (5).

Table 3 - Insulin preparations

Insulin	Onset (min)	Peak(h)	Duration (h)
Lyspro, aspart, glulisine	15 to 30	1 to 2	3 to 6
Detemir	60-120	No peak	19-24
Glargine 100	240 to 3600	No peak	24
Glargine 300	360	No peak	36
Degludec	600 to 720	No peak	42
Human Rapid action	30 to 60	2 to 4	3 to 6
NPH intemediate action	120 to 240	8 to 10	10 to 18

Chronic complications and occupational rules

Beyond the control of raised glucose levels, it is mandatory to regularly screen and manage the risk for development of micro and macrovascular complications: nephropathy, retinopathy, neuropathy and cardiovascular disease. For some individuals it is also necessary to seek modifications for long-term diabetes-related complications. The key message in accommodating an employee with diabetes is to ensure that accommodations are tailored to the individual and effective in helping the individual perform his or her job (6). Specific job requirements-individual's health status interactions must be assessed. Work at heights is contraindicated in presence of repeated episodes of hypoglycaemia. There are no absolute limitations for diabetic workers working shifts/night shifts (1).

Conclusion

Individuals with diabetes can serve as highly productive members of the workforce. Reasonable accommodations can readily be made that allow the vast majority of people with diabetes to effectively perform the job. In recent years, numerous

innovative drugs have become available and it is very important that the occupational physician knows the mechanism of action and the side effects since it could influence the worker's job.

No potential conflict of interest relevant to this article was reported by the authors

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