

# Dysglycaemia, diagnosis and treatment

Giuseppe Derosa<sup>1,2,3,4</sup>, Pamela Maffioli<sup>1</sup>

Correspondence to: Giuseppe Derosa, giuseppe.derosa@unipv.it

ABSTRACT

Euglycaemia is characterized by fasting plasma glucose levels of 70–100 mg/dl, while dysglycaemia is characterized by fasting plasma glucose levels of  $\geq 100$  mg/dl. The term dysglycaemia covers three conditions: impaired fasting glucose (IFG), impaired carbohydrate tolerance (IGT) and type 2 diabetes mellitus. The identification and classification of dysglycaemia and ways to treat it in order to prevent complications are discussed.

## Keywords

Dysglycaemia

*Berberis aristata*

*Ascophyllum nodosum*

*Fucus vesiculosus*

Nutraceutical

Euglycaemia is characterized by fasting plasma glucose levels of 70–100 mg/dl and is usually maintained by the actions of two antagonist hormones: glucagon, which has hyperglycaemic action and is secreted by  $\alpha$ -pancreatic cells, and insulin, which has hypoglycaemic action and is produced by  $\beta$ -pancreatic cells. Muscle cells, adipose tissue and liver cells have receptors for insulin and glucagon. Under normal conditions, after a meal, the pancreas increases insulin secretion to increase glucose utilization by peripheral cells. Insulin binds to receptors in muscle and adipose tissue, which causes the glucose transporter GLUT-4 in the cell cytoplasm to migrate to the cell surface, allowing glucose to enter the cell. The liver also has receptors for insulin: after a meal, insulin binds to these receptors inducing a cascade of signals that inhibit glycogenolysis in favour of glycogen synthesis.

Insulin resistance develops in overweight or obese subjects and is characterized by decreased capacity of the cells of the peripheral organs, particularly the muscles, adipose tissue and liver, to respond to insulin. These cells become less sensitive to insulin, thereby requiring more insulin to perform the same actions. In the initial stage, the pancreas produces more insulin, but with time, it begins to fail to meet the higher insulin demand. When this happens, the patient's blood sugar levels begin to rise above 100 mg/dl. This constant increase in fasting plasma glucose levels, can, over the years, result in type 2 diabetes mellitus if not treated properly.

In the general population, the relationship between complications related to dysglycaemia, including cardiovascular problems, is linear and continuous: the occurrence of cardiovascular events is closely related to deterioration of glycaemic control, in particular post-prandial glucose levels [1]. High post-prandial plasma glucose levels have been shown to be an independent cardiovascular risk factor and a potent inducer of endothelial damage [2, 3].

Dysglycaemia is a significant risk factor for diabetes and contributes to the development of cardiovascular disease. The term dysglycaemia refers to three conditions: impaired fasting glucose (IFG) and impaired carbohydrate tolerance (IGT), which can both evolve into type 2 diabetes mellitus [4].

Dysglycaemia needs to be classified so that the correct therapeutic intervention can be applied: lifestyle modification, possibly with the administration of nutraceuticals in the case of IFG and IGT, or behavioural intervention combined with

<sup>1</sup>Centre of Diabetes and Metabolic Diseases, Department of Internal Medicine and Therapeutics, University of Pavia and Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

<sup>2</sup>Center for the Study of Endocrine-Metabolic Pathophysiology and Clinical Research, University of Pavia, Pavia, Italy

<sup>3</sup>Laboratory of Molecular Medicine, University of Pavia, Pavia, Italy

<sup>4</sup>Center for the Prevention, Surveillance, Diagnosis and Treatment of Rare Diseases, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

pharmacological treatment in the case of diabetes. Dysglycaemia is defined as a fasting plasma glucose level  $\geq 100$  mg/dl. Type 2 diabetes mellitus is diagnosed when two fasting plasma glucose readings are  $\geq 126$  mg/dl or when an occasional blood glucose level is  $\geq 200$  mg/dl, together with polyuria, polydipsia, polyphagia and weight loss in the preceding months.

If fasting plasma glucose levels are  $\geq 100$  mg/dl but  $< 126$  mg/dl, an oral glucose tolerance test (OGTT) should be performed with 75 g of glucose and with determination of blood glucose at time 0 (baseline) and after 120 min.

Based on blood glucose levels 2 hours after glucose loading, the patient will be determined to have:

- IFG if the plasma glucose level after 2 hours is  $< 140$  mg/dl
- IGT if the plasma glucose level after 2 hours is 140–200 mg/dl
- Diabetes mellitus if the plasma glucose level after 2 hours is  $\geq 200$  mg/dl.

An OGTT is normally performed if type 2 diabetes mellitus is suspected, as type 1 diabetes mellitus is usually characterized by blood sugar levels  $\geq 200$  mg/dl, so OGTT is not needed.

In all cases, the first intervention is lifestyle modification with the patient following a healthy diet in order to reduce overweight or obesity, achieve adequate glycaemic control and prevent complications. Daily nutrition should be based on the Mediterranean diet, and consist of  $< 30\%$  fat,  $< 10\%$  saturated fat,  $> 15$  g insoluble and soluble fibre per 1,000 kcal, 45–60% carbohydrates and 15–20% protein. Patients should limit their saturated fat intake to  $< 7\%$  of daily calorie needs; monounsaturated fatty acids, such as olive oil and other vegetable oils, however, are recommended [5]. The patient is also encouraged to increase their physical activity and, in particular, to engage in a minimum of 30–40 min of aerobic activity at least three or four times a week. The patient should also be advised to stop smoking and consuming alcohol.

However, as it is difficult to maintain a healthy lifestyle, especially if the individual has a sedentary job, nutraceuticals have recently been marketed to help patients. Some nutraceuticals have a positive effect on fasting blood glucose levels and insulin resistance [6], with berberine being one of the best studied. Berberine is extracted from *Berberis aristata*, an Indian medicinal plant belonging to the *Berberidaceae* family. It is an isochinolinic alkaloid, and lowers blood glucose levels and improves insulin resistance in diabetic animals and patients partly through activation of

adenosine monophosphate-activated protein kinase (AMPK) and increased phosphorylation of insulin receptor [7].

In a single-blind, randomized, controlled study by Di Pierro *et al* [8], 69 normocholesterolaemic patients with suboptimal control of type 2 diabetes mellitus (HbA<sub>1c</sub> between 7.0% and 9.0%) were randomized to two tablets a day of *B. aristata* (corresponding to 500 mg of berberine) or two tablets a day of *B. aristata/Silybum marianum* for 4 months. Existing therapy was continued during the study. The treatments did not change body weight or anthropometric parameters, but did significantly reduce fasting plasma glucose levels ( $-19.05\%$  for *B. aristata* and  $-18.13\%$  for *B. aristata/S. marianum*) and glycated haemoglobin ( $-7.18\%$  for *B. aristata* and  $-12.35\%$  for *B. aristata/S. marianum*). The benefits of *B. aristata* were confirmed in a report by Derosa *et al* [9] who enrolled 102 Caucasian patients in a double-blind, randomized, placebo-controlled study. Patients were overweight with normal blood pressure,  $\geq 18$  years of age, euglycaemic and hypercholesterolaemic, with total cholesterol levels of 200–240 mg/dl and triglycerides  $< 400$  mg/dl. After a 6-month run-in period during which patients followed a diet and engaged in physical activity, they were randomized to placebo or *B. aristata/S. marianum* extract 588 mg/105 mg twice a day for 3 months. *B. aristata/S. marianum* and placebo were then stopped for 2 months (washout period) and restarted for a further 3 months. The results demonstrated an improved lipid profile with *B. aristata/S. marianum*, while a glucagon stimulation test showed a greater rise in C-peptide levels and a lower increase in blood glucose levels with *B. aristata/S. marianum* compared to placebo, to baseline and to randomization. These data suggest that *B. aristata/S. marianum* could improve  $\beta$ -cell function in insulin resistance. Another nutraceutical containing chromium picolinate and phlorotannins extracted from *Ascophyllum nodosum* and *Fucus vesiculosus*, in a ratio of 95:5, has proved to improve fasting blood glucose levels. The phlorotannins inhibit  $\alpha$ -amylase and  $\alpha$ -glucosidase, thus slowing carbohydrate absorption and demonstrating important hypoglycaemic action in vivo [10, 11] particularly on postprandial hyperglycaemia. At the oral dose of 250–500 mg, this product reaches levels 25–50 times higher in intestinal fluids compared to inhibiting concentrations in vitro, completely inhibiting, in a non-competitive and reversible way, the enzymes degrading carbohydrates [10]. The reversible and non-competitive (not focussed on a catalytic site in competition with the substrate) inhibition of enzyme activity in a rat model results in a reduction in blood glucose levels and in insulinaemia after administration of glucose. The

nutraceutical was administered to humans in one study 30 min before consumption of 50 g of carbohydrate from white bread [11], showing reductions in the incremental area under the curve (iAUC) for glycaemia (−48%) and insulinaemia (−12.1%). Chromium is an essential trace element required for the metabolism of carbohydrates, lipids and proteins. The recommended daily intake of chromium is 40 µg, but the diet often does not provide adequate quantities, also because its bioavailability is low at less than 2%. Chromium is a necessary cofactor for many insulin functions because it promotes binding to insulin receptors in striated muscle cells, adipocytes and hepatocytes, and also promotes the phosphorylation of receptors. These mechanisms contribute to the transport of glucose in the liver, muscle and adipose tissue, thereby improving glucose tolerance.

A recent meta-analysis of 15 controlled clinical trials with a total of 1,690 patients demonstrated the beneficial effects of administering chromium to patients with diabetes. The studies showed that chromium reduces hyperglycaemia, corrects insulinaemia, reduces the need for an oral hypoglycaemic agent, reduces cholesterol and triglyceride levels, and allows better control of body weight and fat mass. The authors of the meta-analysis concluded that the data analyzed support the safety and efficacy of chromium and in particular of chromium picolinate in the control of cholesterol and hyperglycaemia in patients with type 2 diabetes [12].

In conclusion, a diagnosis of IFG or IGT should be an incentive to modify lifestyle in order to postpone a diagnosis of diabetes. A healthy lifestyle is important for achieving this aim and can be supported by the use of nutraceuticals.

### Conflict of interest

The authors declare that they have no conflict of interest.

### REFERENCES

- Bartnik M, Norhammar A, Rydén L (2007) Hyperglycaemia and cardiovascular disease. *J Intern Med* 262:145–156
- Derosa G, D'Angelo A, Salvadeo SA, Ferrari I, Fogari E, Gravina A, Mereu R, Palumbo I, Maffioli P, Randazzo S, Cicero AF (2010) Oral glucose tolerance test effects on endothelial inflammation markers in healthy subjects and diabetic patients. *Horm Metab Res* 42(1):8–13
- Derosa G, D'Angelo A, Salvadeo SA, Ferrari I, Fogari E, Gravina A, Mereu R, Palumbo I, Maffioli P, Randazzo S, Cicero AF (2010) Modification of vascular and inflammation biomarkers after OGTT in overweight healthy and diabetic subjects. *Microvasc Res* 79(2):144–149
- Gerstein HC (2010) More insights on the dysglycaemia-cardiovascular connection. *Lancet* 375(9733):2195–2196
- Derosa G, Limas CP, Macías PC, Estrella A, Maffioli P (2014) Dietary and nutraceutical approach to type 2 diabetes. *Arch Med Sci* 10:336–344
- Derosa G, Maffioli P (2015) Nutraceuticals for the treatment of metabolic diseases: evidence from clinical practice. *Expert Rev Endocrinol Metab* 10(3):297–304
- Derosa G, Maffioli P, Cicero AF (2012) Berberine on metabolic and cardiovascular risk factors: an analysis from preclinical evidences to clinical trials. *Expert Opin Biol Ther* 12(8):1113–1124
- Di Piero F, Putignano P, Villanova N, Montesi L, Moscatiello S, Marchesini G (2013) Preliminary study about the possible glycemic clinical advantage in using a fixed combination of *Berberis aristata* and *Silybum marianum* standardized extracts versus only *Berberis aristata* in patients with type 2 diabetes. *Clin Pharmacol* 5:167–174
- Derosa G, Bonaventura A, Bianchi L, Romano D, D'Angelo A, Fogari E, Maffioli P (2013) *Berberis aristata/Silybum marianum* fixed combination on lipid profile and insulin secretion in dyslipidemic patients. *Expert Opin Biol Ther* 13(11):1495–1506
- Roy MC, Anguenot R, Fillion C, Beaulieu M, Bérubé C, Richard D (2011) Effect of a commercially-available algal phlorotannins extract on digestive enzymes and carbohydrate absorption in vivo. *Food Res Int* 44:3026–3029
- Paradis ME, Couture P, Lamarche B (2011) A randomised crossover placebo-controlled trial investigating the effect of brown seaweed (*Ascophyllum nodosum* and *Fucus vesiculosus*) on postchallenge plasma glucose and insulin levels in men and women. *Appl Physiol Nutr Metab* 36:913–919
- Broadhurst CL, Domenico P (2006) Clinical studies on chromium picolinate supplementation in diabetes mellitus—a review. *Diabetes Technol Ther* 8(6):677–687