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Italian Society for the Study of Diabetes (SID)/Italian Endocrinological Society (SIE) guidelines on the treatment of hyperglycemia in Cushing's syndrome and acromegaly☆

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Abstract *Background:* Hyperglycemia is a common feature associated with states of increased growth hormone secretion and glucocorticoid levels.
Aims: The purpose of these guidelines is to assist clinicians and other health care providers to take evidence-based therapeutic decisions for the treatment of hyperglycemia in patients with growth hormone and corticosteroid excess.
Methodology: Both the SID and SIE appointed members to represent each society and to collaborate in Guidelines writing. Members were chosen for their specific knowledge in the field. Each member agreed to produce—and regularly update—conflicts of interest. The Authors of these guidelines prepared their contributions following the recommendations for the development of Guidelines, using the standard classes of recommendation shown below. All members of the writing committee provided editing and systematic review of each part of the manuscript, and discussed the grading of evidence. Consensus was guided by a systematic review of all available trials and by interactive discussions.

Preface

These Guidelines on the treatment of hyperglycaemia in Cushing's syndrome and acromegaly were endorsed by the Italian Society for the Study of Diabetes (SID) and the Italian Endocrine Society (SIE) to assist clinicians and other healthcare professionals to manage patients affected by these diseases.

The strong biological relationship between Cushing's syndrome, acromegaly and hyperglycaemia prompted these two societies to generate these Guidelines.

The processes involved in generating the Guidelines have been previously described (European Heart Journal 2013, 34:3035–3087). In brief, both the SID and SIE appointed members to represent each society and to collaborate in Guidelines writing. SID and SIE members were chosen for their specific knowledge in the field. Each

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Table 1 Classes of recommendations.

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/ opinion is in favor or usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful	Is not recommended

member agreed to produce—and regularly update—conflicts of interest.

The Authors of these guidelines prepared their contributions following the recommendations for the development of Guidelines, using the standard classes of recommendation shown below (Tables 1 and 2). All members of the writing committee provided editing and systematic review of each part of the manuscript, and discussed the grading of evidence. Consensus was guided by a systematic review of all available trials and by interactive discussions.

These Guidelines are the product of several hours of work, time given freely by the writing committee members. The authors received no funding or remuneration.

Introduction

Hyperglycemia is a common feature associated with states of increased growth hormone secretion and glucocorticoid levels. A sustained excess of these two hormones, which counteract insulin action, is associated with varying degrees of glucose intolerance, including impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and overt diabetes mellitus (DM). The presence of different degrees of altered glucose tolerance is associated with an increased cardiovascular morbidity and mortality associated with acromegaly and Cushing's syndrome. For these reasons, disorders of glucose metabolism should be carefully monitored and treated in these patients. In addition, even in the presence of a normal glucose tolerance, patients should be screened for the appearance of glucose alterations by means of glycated hemoglobin (HbA1c) and/or oral glucose tolerance test (OGTT), particularly when HbA1c measurement are not diagnostic or inconclusive. There are no consensus guidelines on the frequency of screening for diabetes, but clinical judgment based also on the presence of risk factors such as obesity, family history, metabolic syndrome, should prompt for yearly checking for glucose abnormalities.

Table 2 Levels of evidence.

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

The goals of glycemic control in both acromegalic and Cushing's syndrome patients with alterations of glucose metabolism appear to be similar to those of diabetic patients.

Prevalence

Hyperglycemia and acromegaly

In patients with acromegaly, impaired glucose metabolism develops in the presence of concomitant β-cell insufficiency, and a proportion of patients will develop overt DM [1]. The presence of hyperinsulinemia, insulin resistance, glucose intolerance, and DM contributes to the increased cardiac morbidity and mortality in acromegalic patients [2–4]. Moreover, IGT has been found to correlate with the severity of acromegalic cardiomyopathy [5].

The prevalence of impaired glucose metabolism or DM in acromegaly varies between 19 and 56% [6]. In patients with acromegaly, the prevalence of the early stages of impaired glucose regulation (defined as IFG, IGT or their combination) has been shown to vary between 16 and 46% [6–8]; the prevalence of overt DM ranges between 15 and 38% in studies including at least 100 patients [9]. These differences in prevalence may be ascribed to different patient series and ethnicity and, for the older studies, to different diagnostic criteria. Overall, the prevalence of all forms of impaired glucose regulation (IFG, IGT, IFG/IGT and DM) is more than 50% in acromegalic patients, warranting close monitoring and treatment of hyperglycemia. The strongest risk factors for developing any of the possible forms of glucose intolerance include disease duration, higher GH levels, a family history for DM, the presence of hypertension and older age [8–10].

Hyperglycemia and Cushing's syndrome

Hyperglycemia is a frequent complication of Cushing's syndrome. Similar to acromegaly, hyperglycemia occurs as a consequence of an insulin-resistant state coupled with impaired insulin secretion, which are induced by high glucocorticoid levels. Glucocorticoids excess, either exogenous (the most frequent condition) or endogenous, is responsible for the occurrence of chronic complications, such as DM, glucose intolerance, hypertension, dyslipidaemia, obesity, coronary artery disease, and congestive heart failure. Specifically, DM is considered to be a common complication