Editorial

The hypoglycemic side of hypothyroidism

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Hypoglycemia is a not so infrequent condition encountered in endocrine practice. Considered an inevitable (though modifiable) part of diabetes therapy, hypoglycemia occurs fairly often, in both type 1 and type 2 diabetes, in patients on oral hypoglycemic agents and insulin, and in indoor as well as outdoor settings.[1] As the prevalence of diabetes rises, and as we try to control glycemia more aggressively, using the multiple permutations and combinations of antidiabetic drugs available to us, the incidence of hypoglycemia is certain to rise. Apart from this, hypoglycemia is sometimes spontaneous, and may occur without relation to antidiabetic therapy.

Hypoglycemia is basically a mismatch between insulin (whether exogenous or endogenous) and glycemic levels (whether produced by meals or parenteral nutrition). The excessive insulin levels may be due to excessive dosage, increased bioavailability, or enhanced insulin sensitivity. The inappropriate increase in insulin levels leads to a fall in blood glucose levels, which in turn stimulates a series of physiological protective mechanisms. These include a release of glucagon, adrenaline, cortisol, and growth hormone; among others.[1] These physiological responses are linked with symptoms, which can be classified as adrenergic or autonomic, neuroglycopenic, and general (usually glucagon-induced).

Hypoglycemia prevention now occupies center stage in diabetes praxis, as focus moves from a purely efficacy oriented approach to one which aims for safety and tolerability, along with glycemic control. This shift has occurred in parallel with our understanding of the multiple deleterious effects of hypoglycemia on various organ systems; including the heart, brain, and retina.[2]

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Hypothyroidism is one of the most common endocrinopathies worldwide, and its incidence is increasing rapidly.[3] It is frequently found to coexist with both type 1 and type 2 diabetes mellitus.[4,5] Cross-talk between thyroid and diabetes has been the topic of many reviews, which discuss the potential of hyperthyroidism to exacerbate diabetes,[6] and of antidiabetic therapy (metformin) to improve thyroid function.[7] The potential role of hypothyroidism in precipitating hypoglycemia has not been highlighted adequately in current literature. This brief communication aims to discuss the link between hypothyroidism and hypoglycemia, and suggest simple caveats for clinical practice.

Early Literature

Interest in the hypoglycemic effect of hypothyroidism began a century ago, even before insulin was discovered.[8] Hypothyroidism was, by then, a well-known and well-studied entity, and had been differentiated from hypopituitarism. The hypoglycemia of hypothyroidism, dyspituitarism, and Addison's disease was known to be common knowledge.[9] Later, literature clearly highlights the importance of hypothyroidism as a precipitating factor for hypoglycemia, while reporting prolonged hypoglycemia due to exogenously administered insulin in hypothyroid patients.[10]

The correlation between diabetes and hyperthyroidism had also been reported before the advent of the insulin era.[11] In fact, in his 1947 Nobel lecture, Nobel laureate BA Houssay clearly mentions thyroid as one of the 'blood sugar raising' glands (aneterohypophysis, adrenals, thyroid, etc.)[12]

Recent Literature

Recent literature, however, is conflicting and confusing. Some diabetology textbooks choose not to mention

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hypothyroidism as a possible factor in the pathogenesis of hypoglycemia, though they do describe Addison's disease and panhypopituitarism.[1] Major thyroidology textbooks do not mention susceptibility to hypoglycemia as a complication of hypothyroidism.[13] Other modern reviewers, on the other hand, clearly emphasize hypothyroidism as one of the endocrine deficiencies responsible for hypoglycemia.[14] Yet others refute this concept, proposing the theory that if hypothyroidism is accompanied by hypoglycemia, it is in fact a manifestation of panhypopituitarism, rather than primary hypothyroid disease.[15] Yet others tend to trivialize the issue ('although seldom happening, hypothyroid patients can experience hypoglycemia').[16]

Yet, case reports have been published which describe the correlation between hypothyroidism and hypoglycemia, both in infants[17] and in adults.[18] Robust evidence is also available which implicates uncontrolled hyperthyroidism as a cause of poor glycemic control.[19]

Is there a physiologic basis to connect hypothyroidism and hypoglycemia? And if we go a step further, can hypothyroidism be postulated as a precipitating factor for hypoglycemia unawareness?

Pathophysiologic Correlation: Hypothyroidism and Hypoglycemia

Hypothyroidism is linked with various hormonal biochemical and nervous system abnormalities, which may contribute to hypoglycemia.

The condition is linked with low growth hormone and cortisol responses to insulin induced hypoglycemia, and this prevents adequate counter regulatory protection.[20,21] It must be noted that in some cases, pituitary dysfunction may be a consequence of primary hypothyroidism, rather than a cause of thyroid dysfunction. For example, hypothyroidism reduces basal and stimulated growth hormone levels, by acting on both the hypothalamus and pituitary.[21] As it is linked with suboptimal growth hormone response, the recovery from hypoglycemia may be prolonged in hypothyroidism.

Hypothyroid patients have relative adrenal insufficiency, even if they are not associated with primary adrenal failure. There is a blunted hypothalamo-pituitary-adrenal response to hypoglycemia in hypothyroid persons.[22] The reduced cortisol responses to insulin-induced hypoglycemia that are noted in hypothyroidism also worsen hypoglycemia.

The role of gluconeogenesis is reduced in hypothyroidism, both in skeletal muscle and in adipose tissue.[23] Glycogenolysis is also impaired in hypothyroidism.[24] These biochemical defects lead to a delayed recovery from hypoglycemia.

Other abnormalities in hypothyroidism include a reduction in glucagon secretion,[25] reduced effect of glucagon on hepatocytes,[26] and slowing of insulin clearance.[10] Contributory factors also include the effect of hypothyroidism on the gastro intestinal system. It slows gastric emptying[27] and decreases intestinal absorption of glucose as well as portal venous flow.

Modern researchers, on the other hand, have reported the link between subclinical and overt hypothyroidism on one hand, and insulin resistance on the other.[28] Reviewers explain this paradox by contrasting the insulin agonist actions of thyroid hormones, evident in peripheral tissues, with insulin antagonist activity in the liver.[16] The hepatic effects of thyroxin are mediated directly, as well as through the hypothalamus. Variable effects at peripheral and hepatic levels may explain discordant results obtained by different workers.

Therapeutic Implication

The wisdom collated by the pioneers of endocrinology seems to have been lost in modern textbooks. This omission deprives the student of endocrinology of an important clinical practice pearl, viz.: The hypoglycemic side of hypothyroidism. This editorial has tried to highlight a supposedly insignificant aspect of hypothyroidism, which has a significant impact on contemporary diabetology practice. Perhaps the reason for this lack of attention is a lack of clarity regarding the difference between spontaneous hypoglycemia (as seen in panhypopituitarism) and the increased predisposition to hypoglycemia encountered in persons on treatment for diabetes.

The glucoregulatory effects of thyroid hormones carry great clinical significance. Persons with diabetes who report with a sudden increase in frequency or severity of hypoglycemic episodes, not explained by changes in diet, physical activity, or dosage of glucose-lowering drugs, must be evaluated for hypothyroidism.

The symptoms of hypoglycemia may be nonspecific, and may represent subtle neuroglycopenia. A high index of suspicion must be kept in hypothyroid patients on diabetes treatment, as the symptoms of counter regulatory hormone release may be blunted, and there may be an underlying neurocognitive defect in grossly hypothyroid persons.

The clinical implications of the hypoglycemia-prone features of hypothyroidism should be taken into account while

planning antidiabetic therapy. Person with uncontrolled hypothyroidism should be given relatively lower doses of insulin and insulin secretagogues (sulfonylureas). Safer insulin analogues which are linked with a lower incidence of hypoglycemia should be preferred.

In patients on treatment for both thyroid disorders and diabetes, thyroid status should be kept in mind while titrating antidiabetic therapy. Those with an improving thyroid status, or falling serum thyroid stimulating hormone (TSH), may require an increase in dosage of antidiabetic medicines. Similarly, those with worsening hypothyroidism will need a reduction in dosage. This down titration will be needed in patients of Graves' disease who respond rapidly to therapy.

The TSH lowering or potential thyroprotective effect of metformin[7] should be considered while assessing thyroid function reports. Above all, one must follow a panglandular approach while managing any endocrine illness, and not neglect the mature wisdom of clinical endocrinology.

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