

A Review of the Use of Acarbose for the Treatment of Post-prandial Syndrome (Reactive Hypoglycemia)

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Abstract

Introduction: The term “reactive” hypoglycemia, also known as post-prandial hypoglycemia has been loosely defined in the literature. The term refers to the occurrence of autonomic symptoms including weakness, perspiration, hunger, nausea, anxiety and tremors occurring one to two hours after ingestion of a meal. This collection of symptoms has been described in various patient groups including patients with impaired glucose tolerance, dumping syndrome following gastric surgeries (e.g. Nissen fundoplication, Billroth II and Roux en Y gastric bypass) and in patients in whom no specific cause has been identified. These autonomic symptoms have been reported in patients with and without documented hypoglycemia. This suggests that factors other than hypoglycemia may also be involved in the pathogenesis of this disorder.

Data extraction: English-language articles that presented data relevant to the treatment of reactive hypoglycemia were identified in a MEDLINE search from 1966 to 2011. References of these articles and other publications were also reviewed. Search terms were reactive hypoglycemia, functional hypoglycemia, post-prandial hypoglycemia, Nissen fundoplication, Billroth procedure, gastric banding, Roux en Y occurring in association with the term hypoglycemia. Studies were included for review if they evaluated the clinical use of acarbose for the treatment of this syndrome and did not meet our exclusion criteria.

Evidence synthesis: Five case reports and four small controlled trials met our inclusion criteria which examined the use of acarbose in the treatment of reactive hypoglycemia.

Conclusion: We suggest the term Post-Prandial Syndrome (PPS) rather than reactive hypoglycemia since hypoglycemia is often not documented in patients who nevertheless experience postprandial autonomic symptoms. Acarbose is often used for the treatment of postprandial syndrome, but the evidence for its effectiveness is sparse and not definitive. Although acarbose does cause a statistically significant increase in the post-prandial glucose nadir after sucrose ingestion under experimental conditions, the effect is minimal and may not be clinically significant. There are currently no high-quality placebo-controlled clinical trials for the treatment of this syndrome. Further studies are needed to evaluate the potential therapeutic benefit of acarbose in the treatment of PPS.

Introduction

The term “reactive” hypoglycemia, also known as post-prandial hypoglycemia or functional hypoglycemia has been loosely defined in the literature. This phenomenon was first described by Harris in 1924 who reported five cases of hypoglycemia following a meal which he called reactive hypoglycemia [1]. The term refers to the occurrence of autonomic symptoms including weakness, perspiration, hunger, nausea, anxiety and tremors occurring one to two hours after ingestion of a meal. This collection of symptoms has been described in various patient groups including patients’ with impaired glucose tolerance, dumping syndrome following gastric surgeries (e.g. Nissen fundoplication, Billroth II and gastric bypass) and in patients in whom no specific cause has been identified. These autonomic symptoms have been reported in patients with and without documented hypoglycemia. This suggests that factors other than hypoglycemia may also be involved in the pathogenesis of this disorder.

The prevalence of this condition is difficult to ascertain since the symptoms are subjective and there are no formal criteria for diagnosis. To evaluate the prevalence of symptoms attributed to hypoglycemia, a British trial randomly selected 2000 women between the ages of 17-50 and mailed them a health and well-being questionnaire. The women were unaware of the specific focus of the study. The authors report that 37.9% of the participants experienced symptoms attributed to hypoglycemia approximately four times per month [2]. This study did not assess whether the individuals were actually experiencing hypoglycemia but aimed to investigate the percentage of women from a random sample in the UK reporting symptoms which they ascribed to low blood sugar. Only 0.5% of those reporting symptoms in this

survey had sought medical advice for their symptoms. However, other studies have shown that many patients attribute their symptoms to hypoglycemia, but do not have “true hypoglycemia” as defined by the American Diabetes Association requiring plasma glucose value < 3.9 mmol/L (<70 mg/dL) [3]. Thus the term Post-Prandial Syndrome (PPS) maybe a better term than the commonly used “reactive hypoglycemia” since it describes a collection of post-prandial symptoms but does not require documented hypoglycemia.

Several case reports, and a few small placebo-controlled trials have examined the use of acarbose in the treatment of reactive hypoglycemia. Acarbose is an alpha-glucosidase inhibitor which prevents the hydrolysis of di-, tri- and oligosaccharides to monosaccharides in the intestinal brush border, thereby slowing their absorption. This leads to attenuation of post-prandial hyperglycemia which may be related to

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the pathophysiology of this disorder. Although, some studies have reported improvement in symptoms with the use of acarbose, there have been no critical reviews of the limited data supporting the use of this drug in the treatment of reactive hypoglycemia.

The aim of this review is to propose a more comprehensive term, PPS, to encompass the collection of symptoms attributed to this syndrome which provides a more accurate definition since some cases of “reactive hypoglycemia” do include documented hypoglycemia. Further, we aim to critically review the scant evidence for the use of acarbose for the treatment of this syndrome since our literature search demonstrates that this is often the treatment employed for this prevalent condition despite the scarcity of data to support the use acarbose.

Data Extraction Methods

English-language articles that presented data relevant to diagnosis of reactive hypoglycemia were identified in a MEDLINE search from 1966 to 2010. References of these articles and other publications were also reviewed. Search terms were reactive hypoglycemia, functional hypoglycemia, post-prandial hypoglycemia, Nissen fundoplication, Billroth procedure, gastric banding occurring in association with the term hypoglycemia. Studies were included for review if they evaluated the clinical use of acarbose for the treatment of post-prandial hypoglycemia and did not meet our exclusion criteria.

Studies were excluded if they were not in English, or if they included patients less than 18 years of age, had a previously established diagnosis of diabetes, or had other well established causes for hypoglycemia such as cystic fibrosis, insulinoma, insulin administration or intake of oral antihyperglycemic agents. Of the 94 articles that were identified, nine articles were included in the analysis.

The two authors independently abstracted data from the included studies. Disagreements were resolved by discussion.

Discussion

Definition of syndrome

We suggest that Post-Prandial Syndrome (PPS) would be a more appropriate term than “reactive hypoglycemia” to describe the autonomic symptoms experienced by these patients since many patients lack documented hypoglycemia despite experiencing these symptoms. In this context, PPS refers to the occurrence of autonomic signs or symptoms occurring one to two hours after ingestion of a meal with or without documented hypoglycemia. This collection of symptoms has been described in various patient groups including patients’ with impaired glucose tolerance, dumping syndrome following gastric surgeries and in patients in whom no specific cause has been identified.

Acarbose for treatment of PPS

Schrezenmeir and Kasper [4] first reported improvement in PPS with administration of 300 mg/day of acarbose [4]. Since then, a number of case reports and a few trials have been reported in which the use of acarbose for the treatment of PPS was evaluated. Table 1 summarizes the available studies. Of note, no study documented hypoglycemia occurring after the ingestion of complex carbohydrates such as sucrose (Column 9). While all reports indicated short-term relief of symptoms after treatment with acarbose (Column 11), none of them evaluated the use of acarbose over longer periods.

Acarbose for PPS in impaired glucose tolerance patients

Tamura et al. present a case report in which a patient with demonstrated impaired glucose tolerance was experiencing PPS signs and symptoms [5]. However, under experimental conditions, they produced PPS symptoms only after the Oral Glucose Tolerance Test (OGTT), but they could not reproduce PPS signs or symptoms after a sucrose load with or without acarbose. However, after starting the patient on treatment with acarbose before each meal the patient did not experience any further episodes of hypoglycemia. The lack of use

Column	1	2	3	4	5	6	7	8	9	10	11
Study Author(s)	Diagnosis	# of patients	Hypoglycemia symptoms at home	Documented hypoglycemia at home	Hypoglycemia symptoms on OGTT	Documented hypoglycemia on OGTT	Hypoglycemia symptoms with sucrose (or meal tolerance) with acarbose	Hypoglycemia symptoms with sucrose (or meal tolerance) with placebo	Documented hypoglycemia with sucrose (or meal tolerance) with acarbose	Documented hypoglycemia with sucrose (or meal tolerance) with placebo	Improvement on short-term follow up
Gerard et al.	IGT	8	8/8	N/A	8/8	8/8	N/A	N/A	no	no	N/A
	DS	7	7/7	N/A	7/7	7/7	N/A	N/A	no	no	N/A
	idiopat	9	9/9	N/A	9/9	9/9	N/A	N/A	no	yes	N/A
Richard et al.	idiopat	16	16/16	N/A	16/16	13/16	1/16	4/16	0/16	6/16	N/A
Ozgen et al.	idiopat	21	21/21	N/A	18/21	21/21	N/A	N/A	N/A	N/A	21/21
Peter	idiopat	6	6/6	N/A	6/6	6/6	N/A	N/A	N/A	N/A	6/6
Teno et al.	DS	1	1/1	1/1	N/A	N/A	0/1	0/1	0/1	0/1	N/A
Tamura et al.	IGT	1	1/1	1/1	N/A	1/1	0/1	0/1	0/1	0/1	1/1
Imhof et al.	DS	1	1/1	1/1	1/1	1/1	0/1	1/1	0/1	1/1	1/1
Moreira et al.	DS	1	1/1	1/1	N/A	N/A	N/A	N/A	N/A	N/A	1/1
Yamada et al.	DS	1	1/1	N/A	1/1	1/1	N/A	N/A	N/A	N/A	1/1

Table 1: Studies evaluating the use of acarbose for treatment of reactive Hypoglycemia

IGT (Impaired Glucose Tolerance), DS (Dumping syndrome), Idiopat (Idiopathic); OGTT (Oral Glucose Tolerance Test); N/A (Not Applicable). Hypoglycemia is arbitrarily defined as blood glucose < 54 mg/dL
 Studies evaluating the use of acarbose for treatment of reactive hypoglycemia

of a placebo makes it difficult to determine the therapeutic effect of acarbose. Gerard et al. [6] performed a randomized, double-blind, placebo-controlled study looking at the effect of acarbose in treating PPS in patients with documented hypoglycemia on OGTT (glucose < 45 mg/dL). They found that in patients with impaired glucose tolerance, the blood glucose rise occurring after sucrose ingestion was significantly blunted by acarbose. However, again under experimental conditions, the authors state that some patients experienced symptoms during the OGTT, but they do not provide any data about the reproduction of signs or symptoms of hypoglycemia during the sucrose load with or without acarbose. Although the post-prandial insulin and glucose peaks were diminished by the use of acarbose, there was little difference in the glucose nadir between the acarbose and placebo groups. The authors report a nadir of 58 mg/dL in the acarbose group and 52 mg/dL in the placebo group. Their result was statistically significant ($p < 0.05$) however a difference of 6 mg/dL may not be clinically significant.

Acarbose in idiopathic PPS

The study by Gerard et al. [6], also showed that in patients with idiopathic PPS, acarbose reduced the post-prandial blood glucose and insulin peaks compared to placebo [6]. The average of the glucose nadir, in the control group was 46 mg/dL and 63 mg/dL in the acarbose group ($p < 0.001$). The nadir occurred at approximately 2.5 hours with placebo and at 3 hours with acarbose. Again, the authors do not provide any data about the presence of PPS symptoms or improvement after administration of acarbose under the experimental conditions.

In a randomized, double-blinded study by Richard et al. [7], 16 patients with idiopathic PPS were given 45 grams of sucrose per square meter of body surface and either 100mg of acarbose or placebo [7]. Similar to the data of Gerard et al., they show the use of acarbose results in a decreased blood glucose and insulin peak when compared to placebo. The post-prandial glucose nadir in the acarbose group was 55 mg/dL and 49 mg/dL in the placebo group ($p < 0.01$). In the placebo group, 6 patients had a nadir less than 54 mg/dL and 4 of them experienced symptoms of hypoglycemia. In the acarbose group, none of the patients had a nadir of less than 54 mg/dL and only 1 subject complained of hypoglycemia symptoms. The statistical significance of the improvement in symptoms between the two groups is not stated. Again, although there is a statistically significant difference in the glucose nadir between the two groups, this difference of 6 mg/dL may not be clinically significant.

In another study, Peter [8] performed a 75g glucose tolerance test on 6 patients who had idiopathic PPS. All patients had symptomatic hypoglycemia during testing, but the patients were not given acarbose under experimental conditions. They were subsequently treated with 25mg of acarbose with each meal which was increased to 50mg with each meal after 2 weeks and all patients became asymptomatic after 4 weeks of therapy. Neither, acarbose or placebo was used under experimental conditions for evaluating improvement in PPS symptoms. Thus, the data are subjective and difficult to interpret.

Ozgen et al. [9] performed another study on 21 patients with idiopathic PPS. These 21 patients were selected based on having demonstrated a blood glucose value of less than 54 mg/dL on one or more occasions during a 5 hour 75 gram OGTT. During the OGTT 18 out of these 21 patients experienced symptoms of hypoglycemia. Out of these patients, the lowest blood glucose value was 39 mg/dL. After 3 months of treatment with 100 mg of acarbose with each meal, the lowest blood glucose value was 67 mg/dL in the group. No placebo was used in this trial, and the effect of acarbose was not studied under experimental conditions.

Acarbose for PPS in post-surgical dumping syndrome patients

Yamada et al. [10] describe a 78-year old man with a history of partial gastrectomy due to gastric cancer who experienced loss of consciousness twice a week following a meal. After a glucose tolerance test, patient was found to have a peak serum glucose level of 317 mg/dL and a nadir 28 mg/dL which resulted in hypoglycemic coma [10]. Norepinephrine level remained low at < 0.2 ng/mL. After the patient was started on acarbose 100 mg three times a day before each meal, his post-meal serum glucose range remained between 100-200 mg/dL. The patient no longer experienced dumping-related loss of consciousness.

Teno et al. [11] report another case of a 64-year old Japanese man who underwent total gastrectomy and Roux-en-Y anastomosis for gastric carcinoma. He frequently experienced symptoms of hunger, weakness, sweating, dizziness and palpitations which occurred 1-2 hours after a meal. His SMBG levels during these episodes were in the 40-60 mg/dL range. During a meal tolerance test, the patient's peak serum glucose was 333 mg/dL without acarbose, and nadir was 87 mg/dL. The counter-regulatory hormones ACTH, cortisol, epinephrine and dopamine were slightly increased during the hypoglycemia but the norepinephrine level was decreased. Also, there was no glucagon response. The patient was subsequently started on 100 mg of acarbose before each meal and PPS was no longer observed.

Moreira et al. [12] describe a 26-year old woman who experienced episodic postprandial hypoglycemia 16 months after surgery. The authors considered the possibility of Noninsulinoma Pancreatogenous Hypoglycemic Syndrome (NIPHS) and started her on verapamil which resulted in a significant reduction in the frequency of the episodes and decreased the intensity of the symptoms. However, she still had occasional hypoglycemic symptoms, but after the addition of 50 mg acarbose three times a day, there was significant improvement in hypoglycemic episodes.

Imhof et al. [13] also report a case of a 66-year old male with total thoracoabdominal esophagectomy with cervical anastomosis for squamous cell carcinoma of the esophagus. This patient experienced nausea, weakness, dizziness, and qualitative impairment of consciousness occurring in late morning. These symptoms disappeared after carbohydrate ingestion. Treatment with acarbose consistently prevented further symptomatic hypoglycemia. The authors showed that during the 75 g sucrose tolerance test the GLP-1 level was 5 times higher without acarbose.

These case reports show both symptomatic and blood glucose nadir improvements in patients with dumping syndrome after initiation of treatment with acarbose with meals. Neither placebo nor acarbose were tested under experimental conditions in any of the cases.

The study by Gerard et al. [6] also evaluated the therapeutic benefit of acarbose in patients with dumping syndrome. They showed that in patients with dumping syndrome, again acarbose reduced the post-prandial glucose and insulin peaks compared to placebo. The average glucose nadir was 50 mg/dL with placebo and 71 mg/dL with acarbose, however the authors do not state if this was statistically significant.

Pathophysiology of PPS

Insulin secretion is regulated by a plethora of different signals. Post-prandial insulin secretion is affected by glucose and hormones such as GLP-1 and neurotransmitters derived from the nerve endings in the autonomic nerves [14]. The most important neurotransmitters are related to vagus nerve activation which is important during the

early cephalic phase of insulin secretion which occurs following a meal ingestion but before circulating glucose levels increase [14,15]. Acetylcholine is a neurotransmitter released by vagus nerve activation which stimulates insulin secretion [15].

The role of exaggerated insulin response in the pathogenesis of PPS has been shown in some patients [16]. All of the case reports and trials we reviewed have demonstrated a reduced blood glucose and/or insulin peak with the use of acarbose. In patients with impaired glucose tolerance, one possible mechanism for post-prandial hypoglycemia could be excessive delay in insulin secretion occurring while the blood glucose levels are declining [5].

In one study, GLP-1, GIP, and glucagon peaked 30 min after glucose ingestion and were significantly higher in patients with dumping syndrome [17]. The study by Imhof et al. [13] demonstrated that the use of acarbose results in a five-fold decrease in GLP-1 levels compared to without acarbose. In patients with dumping syndrome, rapid gastric emptying resulting in exaggerated plasma concentrations of the insulinotropic hormone GLP-1 and have been implicated in the pathogenesis in patients with dumping syndrome following gastric surgeries. In patients with rapid gastric emptying, the associated plasma volume drop may cause an increase in norepinephrine and other catecholamines inducing autonomic symptoms. These catecholamines may also stimulate the release of glucagon. However, in the case report by Yamada et al. [10], while the blood glucose of the patient dropped to 28 mg/dL during the OGTT, the plasma norepinephrine level remained low. In this particular case, the severity of the hypoglycemia may be a result of lack of response of norepinephrine and possibly other counter-regulatory hormones. This may be another potential mechanism by which patients with dumping syndrome can experience significant hypoglycemia.

In patients with idiopathic post-prandial PPS, stress or anxiety could be a predisposing factor which presumably could enhance catecholamine release following a meal. These people might be abnormally sensitive to normal post-prandial catecholamine release and thus experience symptoms of hypoglycemia without documented hypoglycemia [9]. This may occur due to enhanced sympatho-adrenal response to falling plasma glucose concentrations rather than hypoglycemia itself.

Other factors may be involved as well. Vasoactive Intestinal Polypeptide (VIP) and Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) are neuropeptides that stimulate insulin secretion in a glucose-dependent manner, and they both also stimulate glucagon secretion. VIP and PACAP are known to contribute to the vagally induced insulin secretion [14].

Possible therapeutic mechanism of acarbose in reactive hypoglycemia

In patients with impaired glucose tolerance, the use of acarbose slows the intestinal absorption of carbohydrates, and thus may decrease the time delay between hyperglycemia and insulin response. Thus, the glucose and insulin peaks will better coincide in time and PPS may be avoided.

In patients with dumping syndrome, Imhoff et al. [13] showed that acarbose produced a five-fold decrease in post-prandial GLP-1 levels. GLP-1 increases insulin secretion and decreases glucagon release, and high levels of GLP-1 may be related to the pathogenesis of PPS in patients with dumping syndrome. Thus, a reduction in GLP-1 levels by acarbose may explain its therapeutic effect in these patients. However, in hyperglycemic patients with Type 2 diabetes, ingestion of acarbose

with sucrose load leads to elevated and prolonged GLP-1 release and the therapeutic mechanism is likely secondary to delayed gastric absorption in these patients [18].

Side effects

Long term use of acarbose has been hampered by its intestinal side-effects to carbohydrate malabsorption. However, lowering the dose or using the powder form may prevent these unpleasant side effects [19,20]. None of the cases and trials we reviewed evaluated the side-effects of acarbose in patients with PPS.

Summary

Our review yielded a number of case reports and trials in which the therapeutic benefit was shown with the use of acarbose in patients with PPS. The mechanism of effect is uncertain in these patients. However, since a large number of neuropeptides and hormones are involved in post-prandial insulin secretion and glycemic control, further studies are needed to evaluate the potential pathogenesis of PPS in these patients. VIP and PACAP are two potential neuropeptides which could be involved in this pathogenesis.

From these case reports and trials, some of them have shown a small, but statistically significant increase in the blood glucose nadir with the use of acarbose. However, in most of these studies, this change has been minimal and thus it is less likely to be clinically significant. However, in most of these studies, acarbose has been shown to decrease both the post-prandial glucose and insulin peaks. Perhaps, this rapid peaking in glucose and insulin is related to the pathogenesis and symptomatology of PPS. This hypothesis could be tested by evaluating the effect of other agents as well such as diazoxide which inhibits pancreatic insulin release. This will diminish the insulin peak and perhaps can prevent PPS in susceptible individuals.

Also, most of these studies used OGTT to identify patients with post-prandial hypoglycemia. However, such large glucose loads will not be encountered by patients in usual settings. One study has shown that PPS is uncommon when tested by a more natural stimulus such as a mixed meal rather than by OGTT [21]. Another study suggests that the five-hour OGTT, which was used in some of the reviewed case reports and trials, is unreliable for the diagnosis of PPS, and most patients with symptoms may have emotional disturbances [22].

Future directions

Future studies utilizing a randomized, placebo-controlled, design would provide stronger evidence for the therapeutic effect of acarbose. Because of the subjective nature of the symptoms, variation from subject to subject, and inconsistency in reproducing documented hypoglycemia, the most appropriate study design is a cross-over study using each subject as their own control. Also, rather than OGTT, meal tolerance tests should be performed as they are more representative of physiological conditions. These studies should demonstrate the reproduction of symptoms of PPS under controlled conditions which are alleviated by the use of acarbose compared to placebo. Studies should also aim to have long term follow-up to assess the compliance, side-effects and therapeutic success of the treatment. Such studies would provide better evidence of the therapeutic benefit of acarbose in the treatment of PPS.

Many of the current trials have shown that after treatment with acarbose there have been significant improvements in the signs and symptoms of PPS on short-term follow-up of these patients. However, there has been no long-term follow-up and it is uncertain how long

these patients continued with treatment, and this would be an area for potential future study as well.

Conclusion

There are very few studies available evaluating the use of acarbose for the treatment of PPS. In many of the cases and trials reviewed, the signs and symptoms of PPS could not be reproduced under controlled conditions. In studies where symptoms were reproduced, the use of acarbose for alleviation of these symptoms was not evaluated under controlled conditions. Acarbose was shown to produce a statistically significant increase in the post-prandial glucose nadir in some patients, but this effect was minimal and therefore may not be clinically significant. Further studies are needed to evaluate the potential therapeutic benefit of acarbose in the treatment of PPS, and to study whether or not this benefit is due to placebo effect.

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