Acarbose versus metformin in the treatment of metabolic syndrome

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Abstract

Background: Prevalence of excess weight is increasing after the age of 50 years with a high cost on health in society.

Method: Consecutive patients with excess weight desiring weight loss at and above the age of 50 years were divided into two subgroups according to wishes of patients as to whether they preferred medication or just a diet. Acarbose 100 mg three times daily was initiated in the medication group, orally.

Results: The study included 451 patients, and 81.8% of them were overweight or obese, 71.3% of them had white coat hypertension or hypertension, 57.2% of them had impaired glucose tolerance or diabetes mellitus, and 71.1% of them had dyslipidemia. Initially, 179 patients preferred acarbose. Only 10.6% of patients stopped the acarbose therapy due to excessive flatulence or loose stool. The mean weight loss was 8.3 ± 4.1 kg (0-23) in the acarbose group, whereas it was 0.8 ± 1.3 kg (0-7) in the diet group ($p<0.001$). Although body mass index, low density lipoprotein cholesterol, triglyceride, high density lipoprotein cholesterol, fasting plasma glucose, and systolic and diastolic blood pressure at home decreased with acarbose, significantly ($p<0.001$ for all), none of them decreased with diet, significantly ($p>0.05$ for all).

Conclusion: Due to the high prevalence of excess weight and its consequences after the age of 50 years, acarbose should be initiated in patients with excess weight after the age of 50 years. It should be preferred to metformin due to high prevalence of excessive anorexia induced metformin intolerance in the society.

Key words: Acarbose, metformin, excess weight, metabolic syndrome, chronic endothelial damage, atherosclerosis

Introduction

Due to the prolonged survival of human beings, systemic atherosclerosis may be the major health problem in this century, and its association with some metabolic disorders and smoking and alcohol are collected in the box of metabolic syndrome in the literature (1, 2). The syndrome is characterized by a chronic low-grade inflammatory process on vascular endothelium all over the body (3). The inflammatory process is exaggerated by some factors including aging, physical inactivity, excess weight, smoking, alcohol, chronic infection and inflammation, and cancer (4, 5). The inflammatory process can be slowed down with lifestyle changes, diet, and exercise (6). The syndrome includes some reversible parameters such as physical inactivity, overweight, white coat hypertension (WCH), impaired fasting glucose, impaired glucose tolerance (IGT), hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, smoking, and alcohol for the development of irreversible consequences such as obesity, hypertension (HT), type 2 diabetes mellitus (DM), chronic obstructive pulmonary disease, chronic liver disease, chronic renal disease, peripheral artery disease, coronary heart disease (CHD), and stroke (7-9). The syndrome has become so common all over the world, for example 50 million people in the United States are affected (10). The inflammation induced accelerated atherosclerosis all over the body may be the leading cause of early aging and premature death for both genders all over the world. Physical inactivity induced excess weight may be the major underlying cause of the metabolic syndrome. Excess weight is a disorder characterized by increased mass of adipose tissue. The chronic inflammation inducing endothelial dysfunction probably is the action of excess weight for the increased atherogenicity (11, 12). There are some reports about beneficial effects of acarbose on excess weight and associated disorders in the literature (13, 14). We tried to understand whether or not acarbose has some beneficial effects on excess weight and associated disorders in the present study.

Material and Methods

The study was performed in the Internal Medicine Polyclinic of the Mustafa Kemal University on routine check up patients between March 2007 and July 2011. Consecutive check up of patients with excess weight, desiring weight loss at and above the age of 50 years were taken into the study. They were divided into two subgroups according to wishes of patients as to whether they preferred medication or just a diet. Their medical histories including HT, DM, dyslipidemia, and already used medications were learnt, and a routine check up procedure including fasting plasma glucose (FPG), low density lipoprotein cholesterol (LDL-C), triglyceride, and high density lipoprotein cholesterol (HDL-C) was performed. Patients with devastating illnesses including type 1 DM, malignancies, acute or chronic renal failure, chronic liver disease, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on weight. Body mass index (BMI) of each case was calculated by measurements by the same physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared, and underweight is defined as a BMI of lower than 18.5 kg/m2, normal weight between 18.5-24.9 kg/m2, overweight between 25.0-29.9 kg/m2, and obesity as 30.0 kg/m2 or greater (15). Cases with an overnight FPG level of 126 mg/dL or higher on two occasions were defined as diabetics. An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 110 and 125 mg/dL, and diagnosis of cases with a 2-hour plasma glucose level of 200 mg/dL or greater is DM and between 140-199 mg/dL is IGT (15). Additionally, dyslipidemia is diagnosed when LDL-C is 160 mg/dL or higher and/or triglyceride is 200 mg/dL or higher and/or HDL-C is lower than 40 mg/dL (15). Office blood pressure (OBP) was checked after a 5-minute rest in seated position with a mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2 hours. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases, even in normotensives in the office due to the risk of masked HT after 10 minutes of education about proper blood pressure (BP) measurement techniques (16). The education included recommendation of upper arm while discouraging wrist and finger devices by using a standard adult cuff with bladder sizes of 12 x 26 cm for arm circumferences up to 33 cm in length and a large adult cuff with bladder sizes of 12 x 40 cm for arm circumferences up to 50 cm in length, and taking a rest at least for a period of 5 minutes in the seated position before measurement. An additional 24-hour ambulatory BP monitoring was not required due to the equal efficacy of the method with HBP measurements to diagnose HT (17). Eventually, HT is defined as a mean HBP of 135/85 mmHg or greater, WCH as an OBP of 140/90 mmHg or greater but mean HBP of lower than 135/85 mmHg, and masked HT as an OBP of lower than 140/90 mmHg but mean HBP of 135/85 mmHg or greater (16). The diet was poor for animal sourced foods but rich for vegetables and fruits divided into four to six small meals and snacks everyday in the diet group. To simplify the diet, only one kind of animal sourced diet with a low amount was permitted daily, and fruits were advised before meals to provide saturation. Additionally, foods that are high for sugars such as pastries, candy bars, pies, and candy were restricted. Acarbose 100 mg (Bayer, Turkey) three times daily was initiated for the medication group, orally, but the total dose was reached in the third week by increasing the dose 100 mg per week just to decrease possible side effects of acarbose. Patients were followed up for a period of six-months with four-week intervals. At the end of this period, the acarbose and diet groups were evaluated for the previous and final BMI, LDL-C, triglyceride, HDL-C, FPG, and systolic and distolic HBP values, separately. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 451 cases at and above the age of 50 years, and just 18.1% of them were normal weight with a mean age of 51.9 years (56.0% females), and none of them was underweight. So 81.8% (369 patients) of cases at and above the age of 50 years were overweight or obese. Beside that 71.3% (322 patients) of them had WCH or HT, 57.2% (258 patients) had IGT or DM, and 71.1% (321 patients) had dyslipidemia (Table 1).

Table 1: Characteristics of the study cases at and above the age of 50 years

Variables	Prevalence (n= 451)
Overweight	43.0%
Obesity	38.8%
WCH*	40.1%
HT†	31.2%
IGT‡	23.2%
DM§	33.9%
Hyperbetalipoproteinemia	34.3%
Hypertriglyceridemia	46.1%
Dyslipidemia	71.1%

*White coat hypertension †Hypertension ‡Impaired glucose tolerance §Diabetes mellitus

Initially, 190 patients with excess weight preferred the diet and 179 patients preferred acarbose therapy alone. Only 19 patients (10.6%) stopped the acarbose therapy due to excessive flatulence or loose stool, and 15 patients (7.8%) stopped the diet for various reasons during the follow up period. Finally, the mean age of acarbose therapy patients was 57.5 years and 68.1% of them were female. Similarly, the mean age of the diet cases was 57.1 years and 65.7% of them were female, again. The mean weight loss was 8.3 ± 4.1 kg (0-23) in the acarbose group, whereas it was 0.8 ± 1.3 kg (0-7) in the diet group ($p<0.001$). Although the mean BMI, LDL-C, triglyceride, HDL-C, FPG, and systolic and diastolic HBP values decreased with the acarbose therapy, significantly ($p<0.001$ for all) (Table 2), none of the above parameters decreased with the diet, significantly ($p>0.05$ for all) (Table 3).

Table 2: Comparison of acarbose group before and after therapy

Mean values	Before acarbose therapy	After acarbose therapy	*p*-value
BMI* (kg/m²)	33.3 ± 5.3 (25.0-45.5)	30.2 ± 4.6 (24.3-44.3)	<0.001
LDL-C† (mg/dL)	139.3 ± 31.2 (95-213)	131.3 ± 27.3 (91-209)	<0.001
Triglyceride (mg/dL)	149.3 ± 47.7 (87-402)	139.7 ± 53.3 (76-353)	<0.001
HDL-C‡ (mg/dL)	51.1 ± 10.7 (25-61)	48.2 ± 10.9 (27-59)	<0.001
FPG§ (mg/dL)	129.4 ± 35.3 (109-247)	114.3 ± 28.4 (101-236)	<0.001
Systolic HBP** (mmHg)	145.7 ± 23.6 (111-185)	138.2 ± 21.3 (113-189)	<0.001
Diastolic HBP (mmHg)	96.5 ± 15.3 (69-130)	91.4 ± 14.1 (71-129)	<0.001

*Body mass index †Low density lipoprotein cholesterol ‡High density lipoprotein cholesterol §Fasting plasma glucose **Home blood pressure

Table 3: Comparison of diet group before and after therapy

Mean values	Before diet therapy	After diet therapy	*p*-value
BMI* (kg/m²)	33.3 ± 3.3 (25.0-44.5)	33.0 ± 3.6 (25.0-44.6)	Ns†
LDL-C‡ (mg/dL)	137.2 ± 22.4 (77-231)	136.3 ± 25.3 (81-211)	Ns
Triglyceride (mg/dL)	151.3 ± 43.3 (89-415)	150.4 ± 41.4 (99-425)	Ns
HDL-C§ (mg/dL)	51.7 ± 10.4 (25-60)	51.8 ± 10.3 (29-57)	Ns
FPG** (mg/dL)	127.3 ± 29.2 (107-306)	126.1 ± 31.5 (106-319)	Ns
Systolic HBP*** (mmHg)	141.1 ± 26.3 (117-189)	140.6 ± 25.6 (119-195)	Ns
Diastolic HBP (mmHg)	95.1 ± 17.2 (76-121)	94.9 ± 15.3 (73-137)	Ns

*Body mass index †Nonsignificant ($p>0.05$) ‡Low density lipoprotein cholesterol §High density lipoprotein cholesterol **Fasting plasma glucose ***Home blood pressure

Discussion

Probably obesity is found among one of the irreversible consequences of the metabolic syndrome since after development of obesity, non-pharmaceutical approaches provide limited success to heal obesity. Excess weight may lead to a chronic low-grade inflammation on vascular endothelium all over the body, and risk of death from all causes including cardiovascular diseases and cancers increases parallel to severity of excess weight in all age groups (18). The chronic low-grade inflammation on vascular endothelium may even cause genetic changes in the cells, and the systemic atherosclerotic process may decrease clearance of malignant cells by the immune system, effectively (19). Similarly, effects of excess weight on BP have shown previously that the prevalence of sustained normotension (NT) was significantly higher in the underweight (80.3%) than the normal weight (64.0%) and overweight cases (31.5%, $p<0.05$ for both) (20), and 52.8% of cases with HT had obesity against 14.5% of cases with sustained NT ($p<0.001$) (21). So the major component of the metabolic syndrome may appear as excess weight, which is probably the main cause of insulin resistance, dyslipidemia, IGT, and WCH by means of a chronic low-grade inflammatory process on vascular endothelium (6). Stopping of weight gain with physical activity or diet, even in the absence of a prominent weight loss, probably results with resolution of many parameters of the syndrome (22, 23). But according to our opinion, limitation of excess weight as an excessive fat tissue in and around the abdomen under the heading of abdominal obesity is meaningless; instead it should be defined as overweight or obesity by means of BMI since adipocytes function as an endocrine organ by producing a variety of cytokines and hormones everywhere in the body (6). The resulting hyperactivities of sympathetic nervous system and renin-angiotensin-aldosterone system are probably associated with the chronic low-grade inflammation on vascular endothelium terminating with insulin resistance and an elevated BP. Similarly, Adult Treatment Panel III reported that although some people are classified as overweight with a larger muscular mass, most of them actually have excessive fat tissue, too (15).

Acarbose, a pseudotetrasaccharide, is a natural microbial product derived from culture broths of Actinoplanes strain SE 50. It is an alpha-glucosidase inhibitor. It binds reversibly, competitively, and in a dose-dependent manner to oligosaccharide binding site of alpha-glucosidase enzymes in the brush border of the small intestinal mucosa. It inhibits glycoamylase, sucrase, maltase, dextranase, and pancreatic alpha-amylase. It has little affinity for isomaltase but it does not have any effect on beta-glucosidases such as lactase. As a result, it delays the intestinal hydrolysis of oligo- and disaccharides by alpha-glucosidases mainly in the upper half of the small intestine. Consequently, the absorption of monosaccharides after a meal is delayed and transport through the mucosal surfaces into the circulation is interrupted. On the other hand, it does not have any direct effect on absorption of glucose. Although the acute effect is seen within a few minutes, its effects can last for 3 to 5 hours. Acarbose should be taken with the first bite of a meal. The suppression of alpha-glucosidases is reversible, although pharmacological activity is reliable and persistent with long-term use. Effects with continued use can be maintained over years. Up to now, acarbose failure has not been reported in the literature. Initial therapy with an alpha-glucosidase inhibitor often results with carbohydrates appearing in the colon, where bacterial fermentation occurs, accounting for the frequency and severity of gastrointestinal adverse effects such as flatulence, loose stool, and abdominal discomfort (24). If started at a low dose and titrated slowly, acarbose tends to cause occasional gastrointestinal side effects that are generally tolerable (25). Long-term treatment with acarbose increases colonic bacterial mass, that of lactobacteria in particular. The finally impaired carbohydrate absorption, increased bacterial carbohydrate fermentation, and fecal acidification mimic effects of lactulose or lactilol in patients with liver cirrhosis and portosystemic encephalopathy. So acarbose has a favourable therapeutic profile for the long-term treatment of patients with type 2 DM and liver cirrhosis. Similarly, observed changes in bacterial flora and decreased stool pH and beta-hydroxybutyrate may be associated with antiproliferative effects on epithelial cells in colon that may potentially decrease the risk of carcinogenesis. Acarbose is poorly absorbed and systemic bioavailability is low. After oral administration, less than 2% of the unchanged drug enters into the circulation, with most of the remaining in the lumen of the gastrointestinal tract. Thus there is no need for dosage adjustment in slight renal insufficiency.

After a high carbohydrate meal, acarbose lowers the postprandial rise in blood glucose by 20% and secondarily FPG by 15% (13). Similarly, it lowers fasting and postprandial insulin levels. The initial improvement in blood glucose with acarbose tends to be modest, but efficacy steadily improves with the long-term use, and is maintained over several years without evidence of decreased effect or treatment failure. The beneficial effects of acarbose on serum lipids were also described with a dose-dependent manner (13), since dietary carbohydrates are key precursors of lipogenesis, and insulin plays a central role for postprandial lipid metabolism. Carbohydrate-induced postprandial triglyceride synthesis is reduced for several hours by acarbose, so acarbose lowers plasma triglyceride levels (13). The same beneficial effect is also seen in non-diabetic patients with hypertriglyceridemia, and acarbose reduced LDL-C significantly, but HDL-C remained as unchanged in hyperinsulinemic and overweight patients with IGT (26). Significantly elevated levels of ursocholic acids in the stool appear to be the additive consequence of a decreased rate of absorption and increased intestinal motility due to the changes of intestinal bacteria. Acarbose may lower serum LDL-C by means of an increased fecal bifido bacteria, fecal biliary acids, and LDL-C uptake by the liver. Acarbose together with insulin therapy was identified to be associated with greater improvement in oxidative stress and inflammation in patients with type 2 DM when compared with those who received insulin therapy alone (27). Similarly, acarbose may improve release of glucagon-like peptide-1, inhibit platelet activation, increase epithelial nitrous oxide synthase activity and nitrous oxide

concentrations, promote weight loss, decrease BP, and eventually prevent endothelial dysfunction (13). So acarbose also prevents CHD and other cardiovascular events in patients with excess weight even in the absence of IGT and DM (28, 29). Although some authors reported that the patient population where acarbose is an appropriate selection is limited (30), according to our clinical observations, acarbose should be considered a first-line antidiabetic agent, and is an effective pharmacological option for preventing diabetes in the prediabetic patients. Based on more than 20 years of clinical use of acarbose, numerous studies have not demonstrated any significant toxicity (14). On the other hand, acarbose has not any effect on nutrient intake and patients' eating habits.

Metformin, a biguanide, is currently being used in more than 90 countries worldwide. It is not metabolized in body and 90% of absorbed drug is eliminated as unchanged in the urine. Plasma protein binding is negligible, so the drug is dialyzable. According to literature, antihyperglycemic effect of metformin is largely caused by inhibition of hepatic gluconeogenesis, increased insulin-mediated glucose disposal, and inhibition of fatty acid oxidation (31). Reduction of intestinal glucose absorption has been postulated as another possible mechanism of action (32). Precise mechanism of intracellular action of metformin remains uncertain. Interestingly, 25.9% of patients stopped the metformin therapy due to excessively lost appetite in the previous study (23). Additionally, 14.1% of patients with overweight or obesity in the metformin group rose either to normal weight or overweight group by weight loss without a diet regimen (23). According to our opinion, the major effect of metformin may be a powerful inhibition of appetite. Similar results indicating the beneficial effects of metformin on the BMI, BP, FPG, and lipids have also been reported (33, 34). Probably the major component of the metabolic syndrome may be excess weight and its consequences which can be prevented by suppression of appetite by means of metformin. So treatment of excess weight with metformin will probably prevent not only the IGT or DM but also most of the other consequences of excess weight. Due to the very low risk of life threatening side effects of metformin, which we have never seen in our clinic before, it can be initiated for the majority of cases with excess weight, but clinicians must be careful above the age of 70 years due to risks of comorbid disorders including chronic renal failure, a tendency to develop sepsis, and debility induced weight loss in elders. Although 25.9% of patients stopped the metformin therapy due to excessive anorexia in the above study (23), only 10.6% of patients stopped the acarbose therapy due to excessive flatulence or loose stool in the present study. So acarbose intolerance is significantly lower than metformin intolerance in the society ($p<0.001$). Eventually, acarbose can be used in a larger patient population than metformin according to our clinical experiences, thus we did not put an upper limit of age to start acarbose therapy for patients in the present study.

As a conclusion, due to the high prevalences of excess weight and its consequences after the age of 50 years, and the detected significant benefits of acarbose in prevention of them, acarbose should be initiated in patients with excess weight after the age of 50 years. It should be preferred against metformin due to the high prevalence of excessive anorexia induced metformin intolerance in society.

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