PANMINERVA MED 2010;52(Suppl. 1 to No 2):27-32

Kidney function in metabolic syndrome may be improved with Pycnogenol®

S. STUARD [1], G. BELCARO [2], M. R. CESARONE [2], A. RICCI [2], M. DUGALL [2], U. CORNELLI [2], G. GIZZI [2], L. PELLEGRINI [2], P. J. ROHDEWALD [3]

[1]*Nephrology Unit, L'Aquila Hospital, L'Aquila, Italy*
[2]*Labs Irvine3*
Department of Biomedical Sciences
Chieti-Pescara University, Pescara, Italy
[3]*Institute of Pharmaceutical Chemistry*
University of Münster, Münster, Germany

Aim. **We investigated benefits of Pycnogenol® as an adjunct to hypotensive medication in metabolic syndrome patients with micro-albuminurea.**
Methods. **Fifty eight patients were treated with Ramipril and a subgroup received Pycnogenol in addition for six months. Colour Doppler duplex ultrasound was employed for cortical flow measurements.**
Results. **Blood pressure decreased with Ramipril from 188.8/95.2 to 128.2/90.2, with additional Pycnogenol from 189.3/97.2 to 122.2/85.3 (P<0.05). Kidney function improved in both groups, with 24 hour urinary albumin decreasing from 88.8 to 68.9 mg with Ramipril and from 89.3 to 42.2 mg with additional Pycnogenol (P<0.05). In both groups treatment lowered serum creatinine, with combination treatment being significantly more effective. Cortical flow velocities significantly increased with Ramipril from systolic 17.2 ± 3.1 to 23.8 ± 2.0 cms^{-1} and diastolic 4.2±2.8 to 2.0±3.1 cms^{-1}. The addition of Pycnogenol was more effective, improving cortical flow from systolic 18.2±2.2 to 27.2±2.9 cms^{-1} and diastolic 4.1±2.2 to 9.8±2.1 cms^{-1} (P>0.05). C-reactive protein (CRP) levels decreased marginally with Ramipril, but significantly with Pycnogenol from 2.17 to 1.62 mg/dL. Pycnogenol significantly lowered fasting blood glucose to 102.3 ± 11.2 mg/mL and HbA1c to 6.9 ± 0.3 %. The Pycnogenol group showed a significantly lowered BMI, from baseline 26.5±0.9 to 25.0±1.2 kgm^{-2}, without reaching statistical significance versus control. Only a limited improvement of blood lipid profile was found in both groups.**
Conclusion. **Pycnogenol should be further investigated for kidney function.**

KEY WORDS: Kidney function tests - Metabolic syndrome - Pycnogenol - Ramipril.

Pycnogenol® (trade mark of Horphag Research) is an extract of French maritime pine bark (*Pinus pinaster* Ait), standardised to 70±5% procyanidins in accordance to United States Pharmacopeia (USP). Further to the procyanidins the extract bears catechin, taxifolin and a range of phenolic acids representing cinnamic- and benzoic acid derivatives.[1]

Pycnogenol has been shown in human pharmacological as well as in clinical studies to have circulatory and anti-inflammatory activities.[2-4] The improvement of endothelial function with Pycnogenol was shown to decrease blood pressure in individuals with essential hypertension.[5, 6] These effects have been attributed to vaso-dilatation which is associated with an improved level of perfusion as previously shown in peripheral circulation, the retina and the kidneys.[7, 8]

In individuals presenting with metabolic syndrome, elevated systolic blood pressure and blood glucose are the main factors related to the development of kidney micro-albuminuria. One of the largest epidemiological studies, the Australian Diabetes Obesity and Lifestyle Study (Aus-Diab), clearly showed the interaction of both factors in the prevalence of micro-albuminuria.[9] Whereas blood pressure is the major determinant of micro-albuminuria, the glucose level is the major determinant of renal insufficiency.[10] In this regard Pycnogenol may represent a potentially inter-

Conflict of interest.—None.

Corresponding author: P. J. Rohdewald, PhD, Westfälische Wilhelms Universität, Münster, Hittorfstr. 58-62, 48149 Münster, Germany. E-mail: rohdewa@uni-muenster.de

esting adjunct to hypertensive medication in patients with metabolic syndrome. Pycnogenol potently inhibits α-glucosidase and was shown to dose-dependently lower blood glucose in diabetic patients.[6, 11] The latter group by coincidence found a decreased urinary albumin after three month supplementation with Pycnogenol using a semi-quantitative "dipstick" technique. We previously described kidney-protective effects with Pycnogenol in hypertensive subjects.[7] The aim of this study was to investigate kidney protective effects of Pycnogenol taken as an adjunct to ACE-inhibitor Ramipril in metabolic syndrome patients.

Materials and methods

For this study we recruited hypertensive patients with diabetic syndrome who did not take any hypo-glycaemic medications. All patients gave their informed consent in writing. Subjects could withdraw from the study for any reason at any time.

As inclusion criteria, subjects had to present with hypertension (>150/90 mmHg) without taking hypotensive medication before participation in the trial. Body mass index was required to be > 25 kgm^{-2}, and fasting blood glucose >100 mg/mL with HbA_{1c}>7%. Altered kidney function (plasma creatinine) was present in all patients and was associated mainly to insufficient or incorrect treatment of hypertension and inadequate management of cardiovascular risk factors. Patients present with elevated total cholesterol >200 mg/dL. Atherosclerosis (plaques with stenosis at the fermoral or carotid bifurcation) or increase in intima media thickness (IMT) was present in patients.

All participants were instructed to follow a healthier lifestyle with dietary improvements (low sodium), moderate exercise and effective management of risk factors including body weight.

Exclusion criteria were cases of kidney artery stenosis or kidney artery alterations. Patients with severe chronic hyperglycaemia requiring medication were excluded from this study.

Treatment regimen

All patients started treatment with ACE-inhibitor at inclusion under control of their general practitioner. Only Ramipril was used in patients to standardise treatment as much as possible. All patients received a standard dosage of 5 mg Ramipril twice a day.

A subgroup of these patients was equipped with sufficient Pycnogenol for daily supplementation. Tablets with 50 mg Pycnogenol, manufactured by GEFA (Chateaugiron, France) were taken three times a day at approximately 8 am, 4 pm and 10 pm for a total daily dosage of 150 mg Pycnogenol.

Investigation of blood pressure, blood and urine specimen

Patients were investigated at baseline and after six months of treatment. Fasting blood was drawn for standard blood rheology and chemistry analysis. Systolic and diastolic blood pressure and heart rate were monitored in the morning. Twenty-four hour urine was collected and investigated for albumin using standard techniques.

Cortical flow measurements using colour Doppler Duplex ultrasound

Cortical flow measurements were carried out using colour Doppler Duplex ultrasound as previously described.[7] After imaging the kidney with an anterior approach in B-mode, the blood flow velocity of kidney arteries was observed. Cortical flow was measured by placing the sample volume cursor at the level of the most external layer of the kidney, 1 cm from the edge of the ultrasound image, opposite of the vessel entrance into the organ. The flow imaging system, was used only for positioning of the instrument. Then the instrument was reversed to B-mode using gray scale imaging and frame rate at a more efficient level. Blood flow velocity and its components were measured at three levels: at each of the two kidney poles and at the cortical area opposite the vessel entrance into the kidney. During this procedure taking 30 to 40 seconds patients had to avoid any body movement. An average of three measures each for systolic component, diastolic component and an average diastolic to systolic component were obtained, respectively.

Statistical analysis

In view of the possible variability, especially of kidney cortical flow, measurements were made in controlled, standardised conditions to avoid variability wherever possible. Consequently, measurements were made 20 minutes after rest in supine position, before 11 am and at standard distance from drug intake. We

included at least 20 participants for each study group with at least 30% females included into each group. A post-treatment flow velocity variation >5% and signs and symptoms was considered significant (P<0.05) to define improvement due to treatments of differences between groups. The evaluation of kidney cortical flow, even in standardized clinical/environmental and individual conditions, cannot be considered statistically regularly distributed. Therefore, non-parametric statistic tests (Mann-Whitney U-test and the analysis of the variance among groups) were used in the final evaluation of treatment-dependent statistical data. A separate group independently conducted data collection and elaboration and the final statistical analysis. The statistician was not aware of the technical details of the study protocol.

Results

The two groups were comparable in view of gender and age (Table I). All investigated metabolic syndrome parameters as well as the manifestation of early kidney function impairment was comparable in both groups (Table II).

As expected with Ramipril medication the blood pressure was substantially and significantly lowered after six months as presented in Table II. Adding Pycnogenol as an adjunct to the Angiotensin-Converting-Enzyme (ACE)-inhibitor medication significantly further lowered systolic and diastolic blood pressure as compared to the group taking Ramipril alone. While the average systolic and diastolic blood pressure in the Ramipril group remained borderline high (128.2/90.2 mmHg) the values in the group taking Pycnogenol in addition to the ACE-inhibitor presented essentially normal blood pressure values. Noteworthy is the diastolic pressure achieved in this group of 85.3 mmHg, which is well below the threshold of 90 mmHg. The heart rate was lowered in both significantly compared to baseline values, though there was no difference between the groups.

The total cholesterol as well as the HDL values improved in both groups significantly which may be attributed largely to the healthier diet proposed to patients. There was no significant difference between the two groups (Table II).

Both the fasting blood glucose as well as the HbA_{1c} levels significantly decreased in both groups after six months of treatment (Table II). Compared to Ramipril alone the addition of Pycnogenol significantly further lowered fasting blood glucose and allowed to reach normal HbA_{1c} levels below 7% (P<0.05). The average Body Mass Index (BMI) did not change in the group taking Ramipril only. The group taking Pycnogenol presented with a 5.7% decreased BMI after six months, which was significant compared to baseline values. However, with an average BMI value of 25.8 kgm^{-2} they were still overweight. Also the decreased BMI in the Pycnogenol group did not reach statistical significance *versus* the parallel group.

The kidney function improved in both groups as judged by a significant reduction of urinary albumin col-

TABLE I.—*Patient demographics.*

	Total number completed	Male to female ratio	Age±SD (years)
Ramipril only	27	15+12	58.2±8.3
Ramipril plus Pycnogenol®	31	16+15	59.1±8.2

TABLE II.—*Variation in blood pressure, heart rate, body mass index, urinary albumin, blood sugar and cholesterol. The asterisk indicates statistical significant changes compared to baseline, the double dagger indicates statistical significant between groups after six months treatment.*

	Ramipril only		Ramipril + Pycnogenol		p<0.05
	Baseline	6 months	Baseline	6 months	
systolic BP [mmHg]	188.8±9.3	128.2±6.9 *	189.3±11.3	122.2±7.3 *	‡
diastolic BP [mmHg]	95.2±6.2	90.2±6.0 *	97.2±6.3	85.3±5.1 *	‡
heart rate [s-1]	88.9±9.3	75.3±6.1 *	89.1±7.2	74.2±5.2 *	NS
fasting glucose [mg/mL]	138.2±12.1	109.2±10.2*	135.6±13.2	102.3±11.2*	‡
HbA1c [% of Hb]	7.9±0.4	7.4±0.5 *	7.8±0.5	6.9±0.3 *	‡
BMI [kgm-2]	26.6±1.4	26.5±1.0	26.5±0.9	25.0±1.2 *	NS
total cholesterol [mg/dL]	238.7±20.3	198.8±21.3*	236.2±22.2	193.3±20.2*	NS
HDL [mg/dL]	43.3 (5.2)	45.1 (5.2) *	43.8 (3.9)	46.3 (3.8) *	NS
urinary albumin [mg/24h]	88.8±10.1	68.9±11.8 *	89.3±15.2	42.2±10.8 *	‡

TABLE III.—*Variations in kidney cortical flow velocity measured by colour duplex Doppler. The diastolic component depicts the ratio of median diastolic flow to systolic flow velocity presented as percentage (x100). These percentage values are given as median and range of patients in the two groups.*

	Ramipril only		Ramipril + Pycnogenol		p<0.05
	Baseline	6 months	Baseline	6 months	
Systolic flow [cm/s]	17.2±3.1	23.8±2.0 *	18.2±2.2	27.2±2.9 *	‡
Diastolic flow [cm/s]	4.2±2.8	8.2±2.0 *	4.1±2.2	9.8±2.1 *	‡
Diastolic component [%]	24.4 (12-29)	34.5 (21-44)*	22.5 (11-29)	36.0 (23-52)*	‡

TABLE IV.—*Variation in parameters of blood rheology, blood chemistry and liver enzymes. The asterisk indicates statistical significant changes compared to baseline, the double dagger indicates statistical significant between groups after six months treatment.*

	Ramipril only		Ramipril + Pycnogenol		p<0.05
	Baseline	6 months	Baseline	6 months	
ALAT [U/L]	46.2±7.7	45.2±3.1	47.8±3.3	46.3±3.2	NS
ASAT [GOT]	45.3±10.2	45.8±3.5	46.2±9.3	44.3±6.1	NS
GAMMA GT [U/L]	66.3±8.2	68.3±6.1	68.8±3.2	67.2±8.2	NS
Alk. phosph. [U/L]	59.8±12.1	59.3±6.2	58.7±3.2	58.3±4.3	NS
Ser. creatinine [mg/dL]	1.73±2.2	1.42±0.5 *	1.83±2.6	1.25±0.6 *	‡
Erythrocytes [x1012/L]	4.90±0.29	4.93±0.31	4.91±0.33	4.88±0.22	NS
Leukocytes [x109/L]	5.6±1.3	5.4±1.2	5.5±1.4	5.4±1.1	NS
Platelets [x109/L]	263±23	266±21	260±22	262±82	NS
Fibrinogen [mg/dL]	563.3±42.2	462.3±46.2*	568.6±39.2	426.2±37.8*	‡
CRP [mg/dL]	2.21±0.3	2.13±0.31	2.17±0.31	1.62±0.22 *	‡
INR [ratio]	1.1±0.2	1.07±0.3	1.08±0.2	1.06±0.2	NS

lected over 24 hours (Table II). With Ramipril alone urinary albumin decreased by 22% after six month treatment. The addition of Pycnogenol to the ACE-inhibitor decreased urinary albumin by 52.7%, which was statistically significant *versus* medication alone (P<0.05). However, both groups did not reach the threshold value of 30 mg albumin collected per 24 hours.

The cortical flow velocities were significantly higher after treatment with Ramipril (Table III), with diastolic flow almost doubled. The group taking Pycnogenol in addition to the ACE inhibitor showed significantly higher velocities for both diastolic (+19.5%) and systolic (+14%) flow. The diastolic component, the ratio of diastolic to systolic flow velocity expressed as percentage, significantly increased in both groups compared to baseline. The diastolic component with combination treatment was found to be significantly higher than with Ramipril alone.

An improved glomerular filtration rate is suggested from lowered serum creatinine levels, which were moderately elevated at baseline. In both groups serum creatinine decreased significantly compared to baseline values (Table IV). The values in response to combination treatment were significantly lower than with Ramipril alone.

The plasma C-reactive protein levels were moderately elevated in our patients with values above 2 mg/dL. No significant change was found in the group taking Ramipril, whereas the group taking Pycnogenol showed a statistical significantly lowered CRP level (1.62 mg/dL) compared to Ramipril alone. Fibrinogen levels significantly decreased in both groups compared to baseline. The values for combination treatment were significantly lower than with Ramipril alone.

Parameters for blood rheology and liver enzymes were within healthy ranges in both groups. Clotting factors appear to be unaltered as International Normalized Ration (INR) did not change. No adverse effects occurred during the trial and tolerance was very good.

Discussion

Kidney protection is a very important issue in advanced hypertension management and treatment.

Hypertension and kidney flow alterations are interrelated as hypertension may be both a consequence of reduced kidney perfusion as well as a cause of vasospasm and decreased flow and perfusion. Traditional cardiovascular risk factors, including advanced age, diabetes mellitus, hypertension and dyslipidemia, have an important role in the progression of cardiovascular disease in patients who have a reduced glomerular filtration rate, especially in those with mild-to-moderate kidney disease.[12] Kidney disease related to metabolic syndrome represents a growing public health problem especially in certain ethnic groups.[13-14]

We have shown in a previous study that using the nutritional supplement Pycnogenol as an adjunct to ACE-inhibitor may further improve kidney flow and kidney function.[7] Furthermore, another group has recently described lowered urinary albumine in hypertensive type II diabetic patients after three month supplementation of Pycnogenol.[6] This group described better blood pressure and blood glucose control. Indeed, Pycnogenol offers an interesting pharmacological profile for cardiovascular risk factors as it was described to improve endothelial function and consequently reduce hypertension.[2, 5, 15] We have previously described anti-edema effects of Pycnogenol in hypertensive patients on medication with ACE-inhibitors or calcium channel blocker nifedipine.[16] In the study presented here we found a further lowered blood pressure with Pycnogenol taken in addition to ACE-inhibitor. This is in congruence with earlier studies showing further blood pressure lowering with Pycnogenol taken in addition to ACE-inhibitors or calcium channel blocker.[6, 7, 15]

In this study we investigated in detail the effects of Pycnogenol in metabolic syndrome patients presenting with early manifestations of kidney problems. Patients with metabolic syndrome live at a particular risk of progressively deteriorating kidney function because of the large number of cardio-vascular risk factors involved. Our study shows that Pycnogenol is effective for better hypertension control in patients with metabolic syndrome. Pycnogenol taken in addition to ACE-inhibitor significantly further lowered diastolic and systolic blood pressure. More importantly our study demonstrates significant kidney protective benefits with lowered urinary albumin and serum creatinine. The clustering of various cardiovascular risk factors in metabolic syndrome patients with kidney disease is described to coincide with elevated blood CRP levels.[17] The CRP levels in our patients were only moderately elevated with in average 2.2 mg/dL. The CRP level was only lowered in Pycnogenol-treated subjects which may results from the general anti-inflammatory activity shown for this extract in human pharmacological studies, as well as in other pathologies such as osteoarthritis.[3, 4, 18] We speculate, however, that the overall improvement of cardiovascular risk factors and kidney function found for the combination of Pycnogenol with standard ACE-inhibitor in consequence decreased pro-inflammatory stimuli.

Hypertension and kidney flow alterations are closely inter-related as hypertension may be both a consequence of a reduction in kidney perfusion but also cause vaso-spasms and decreased flow and perfusion.[7, 19] In our study Pycnogenol led to a remarkable improvement of cortical kidney flow and perfusion, especially in view of the relatively short period of six months.

Although the occurrence of renal complications is relatively common, it may usually be effectively counteracted by a good timely management of hypertension and hyperglycemia to avoid passages to more advanced stages. Further to the amelioration of endothelial function, Pycnogenol showed a significant blood glucose lowering effect in our study. The hypoglycaemic effect of Pycnogenol has been attributed to the high molecular weight procyanidins present in the extract which potently inhibit alpha-glucosidase.[20] Pycnogenol has been demonstrated in previous studies to dose-dependently and significantly lower fasting and post-prandial blood glucose in diabetic patients, also those on hypo-glycaemic treatment with sulfonylurea and/or metformin or thiazolidinediones.[6, 11, 21] An interesting, though coincidental finding of our study is the significant reduction of body mass index in the Pycnogenol treated group *versus* baseline values. This may be a result of the alpha-glucosidase inhibition as this may prolong satiety and in consequence allow for decreased total caloric intake. In essence α-glucosidase inhibition resembles a low-glycaemic index which was recently suggested to contribute for controlling caloric intake.[22] However, the decreased BMI found for the Pycnogenol group did not reach significance *versus* the parallel group.

This preliminary evaluation suggests valuable effects with Pycnogenol for individuals with metabolic syndrome especially for kidney-protection. The benefits shown here should be investigated in a larger trial with

a longer duration as treatment options for chronic kidney problems are limited. Pycnogenol may represent a valuable tool for people affected.

References

1. Rohdewald P. A review of the French maritime pine bark extract (Pycnogenol®), a herbal medication with a diverse pharmacology. Int J Clin Pharmacol Ther 2002;40:158-68.
2. Nishioka K, Hidaka T, Takemoto H, Nakamura S, Umemura T, Jitsuiki D *et al.* Pycnogenol®, French maritime pine bark extract, augments endothelium-dependent vasodilation in humans. Hypertens Res 2007;30:775-80.
3. Grimm T, Chovanová Z, Muchová J, Sumegová K, Liptáková A, Duracková Z *et al.* Inhibition of NF-κB activation and MMP-9 secretion by plasma of human volunteers after ingestion of maritime pine bark extract (Pycnogenol®). J Inflamm 2006;3:1-15.
4. Canali R, Comitato R, Schonlau F, Virgili F. The anti-inflammatory pharmacology of Pycnogenol in humans involves COX-2 and 5-LOX mRNA expression in leukocytes. Int Immunopharmacol 2009;9:1145-9.
5. Hosseini S, Lee J, Sepulveda RT, Fagan T, Rohdewald P, Watson RR. A randomized, double blind, placebo controlled, prospective, 16 week crossover study to determine the role of Pycnogenol® in modifying blood pressure in mildly hypertensive patients. Nutr Res 2001;21:67-76.
6. Zibadi S, Rohdewald PJ, Park D, Watson RR. Reduction of cardiovascular risk factors in subjects with type 2 diabetes by Pycnogenol supplementation. Nutr Res 2008;28:315-20.
7. Cesarone MR, Belcaro G, Stuard S, Schonlau F, Di Renzo A, Grossi MG *et al.* Kidney flow and function in hypertension: Protective effects of Pycnogenol® in hypertensive subjects – A controlled study. J Cardiovasc Pharmacol Ther 2010;15:41-6.
8. Steigerwalt R, Belcaro G, Cesarone MR, Di Renzo A, Grossi MG, Ricci A *et al.* Pycnogenol® improves microcirculation, retinal edema and visual acuity in early diabetic retinopathy. J Ocul Pharmacol Ther 2009;25:537-40.
9. Atkins RC, Briganti EM, Zimmet PZ, Chadban SJ. Association between albuminuria and proteinuria in the general population. The AusDiab Study. Nephrol Dial Transplant 2003;18:2170–4.
10. Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V *et al.* The metabolic syndrome and chronic kidney disease in US adults. Ann Intern Med 2004;140:167-74.
11. Liu X, Zhou HJ, Rohdewald P. French maritime pine bark extract Pycnogenol® dose-dependently lowers glucose in type II diabetes patients. Diabetes Care 2004;27:839.
12. van der Zee S, Baber U, Elmariah S, Winston J, Fuster V. Cardiovascular risk factors in patients with chronic kidney disease. Nat Rev Cardio 2009;6:580-9.
13. Lora CM, Daviglus ML, Kusek JW, Porter A, Ricardo AC, Go AS *et al.* Chronic kidney disease in United States Hispanics: a growing public health problem. Ethn Dis 2009;19:466-72.
14. Jang SY, Kim IH, Ju EY, Ahn SJ, Kim DK, Lee SW. Chronic kidney disease and metabolic syndrome in a general Korean population: the Third Korea National Health and Nutrition Examination Survey (KNHANES III) Study. J Public Health (Oxf) 2010 Jan 8. [Epub ahead of print].
15. Liu X, Wei J, Tan F, Zhou S, Würthwein G, Rohdewald P. Pycnogenol®, French maritime pine bark extract, improves endothelial function of hypertensive patients. Life Sci 2004;74:855-62.
16. Belcaro G, Cesarone MR, Ricci A, Cornelli U, Rohdewald P, Ledda A *et al.* Control of edema in hypertensive subjects treated with calcium antagonist (nifedipine) or angiotensin-converting enzyme inhibitors with Pycnogenol. Clin Appl Thromb Hemost 2006;12:440-4.
17. Filiopoulos V, Vlassopoulos D. Inflammatory syndrome in chronic kidney disease: pathogenesis and influence on outcomes. Inflamm Allergy Drug Targets 2009;8:369-82.
18. Belcaro G, Cesarone MR, Errichi S, Zulli C, Errichi BM, Vinciguerra G *et al.* Variations in C-reactive protein, plasma free radicals and fibrinogen values in patients with osteoarthritis treated with Pycnogenol. Redox Rep 2008;13:271-6.
19. Baig SZ, Coats WC, Aggarwal KB, Alpert MA. Assessing cardiovascular disease in the dialysis patient. Adv Perit Dial 2009;25:147-54.
20. Schäfer A, Högger P. Oligomeric procyanidins of French maritime pine bark extract (Pycnogenol®) effectively inhibit alpha-glucosidase. Diabetes Res Clin Pract 2007;77:41-6.
21. Liu X, Wei J, Tan F, Zhou S, Würthwein G, Rohdewald P. Antidiabetic effect of Pycnogenol French maritime pine bark extract in patients with diabetes type II. Life Sci 2004;75:2505-13.
22. Belcaro G, Cesarone M, Silvia E, Ledda A, Stuard S, Dougall M *et al.* Daily consumption of Reliv Glucaffect for 8 weeks significantly lowered blood glucose and body weight in 50 subjects. Phytother Res 2009;23:1673-7.