Medicina Sportiva
Med Sport 16 (4): 131-139, 2012
DOI: 10.5604/17342260.1024761

ADAPTATION OF THE ENDOGENOUS INSULIN SECRETION IN NON-INSULIN-DEPENDENT DIABETES BY AN INDIVIDUAL SPORT THERAPEUTIC INTERVENTION – A PILOT STUDY

Thomas Küpper[1,2(A,D,E)], Victoria Jacobson[1(B,C,D)], Sarah Müller[1(B,C,D)], Michael Müller[3,4(B,C,D)], Carolin Westphal[1(B,C,D,E)]

[1]Institute of Occupational and Social Medicine, RWTH Aachen University, Aachen, Germany
[2]Medical Commission of the Union Internationale des Association d'Alpinisme (UIAA), Bern, Switzerland
[3]Practice for General Medicine and Sports Medicine, Freilingen, Germany
[4]Go21 Centre for Therapy and Sport, Herschbach, Germany

Abstract

Objective: To evaluate the effect of a multimodular therapy concept (endurance training, strength training, and diet) on proinsulin in patients with metabolic syndrome and non-insulin dependent diabetes.

Methods: Prospective cohort study (n = 22), pre- post-evaluation. Data evaluated: BMI, HbA1c, proinsulin, body fat, serum glucose. Observation period three months.

Results: Proinsulin showed a tendency to normal values (n.s.). When those patients who took metformin (n = 7) only, the effect was significant (P < 0.05). BMI, body fat and body weight decreased significantly (P < 0.001). HbA1c did not change significantly.

Conclusions: Although the effect of decrease of body mass may be partially camouflaged because there was an increase of muscle mass (heavier than fat), the concept has been proven to be an effective strategy to decrease several risk factors on metabolic syndrome. Further investigations are necessary to detect subgroups of patients who may have the optimal benefit and more data are necessary to establish an optimized structure of the training for the patients. Such studies should cover longer observation periods (6 months or more).

Key words: *metabolic syndrome, diabetes, sport, proinsulin, insulin*

Introduction

In 2005 the International Diabetes Federation has defined the metabolic syndrome (MS) as abdominal adipositas with a waist circumference of 94 cm or more for European men or at least 80 cm for European women, in combination with at least two of the following factors: triglycerides >150 mg/dl, HDL cholesterol <50 mg/dl in females or <40 ml/dl in males, increased blood pressure (>130/85 mmHg) and either increased fasting plasma glucose levels (>100 mg/dl), a non-insulin-dependent diabetes or a previous of one of these disturbances. Normally several of these factors, everyone of which an independent cardiovascular risk factor, may be found at the same patient. But MS is more than a risk factor: it significantly decreases the quality of life of the patients [1].

About 5% of the German population suffers from diabetes (~90% type II diabetes) and it was estimated that in about a third of them the disease was never diagnosed [2]. The annual increase of the prevalence of diabetes in Western Europe is 10% [3]. These patients have a 2- to 6-fold risk for coronary heart disease (CHD) compared to non-diabetic persons [4, 5]. Statistically their risk is as high as those of patients with a myocardial infarction in their history [5-7]. Recent data support these results (e.g. [8]). The other way around 30-67% of those patients who suffer from CHD (diagnosis by angiography) show an impaired glucose tolerance according to WHO criteria [5, 9, 10].

Table 1. *WHO criteria for obesity [29]*

WHO class	BMI [kg/m^2]
Underweight	<18.5
Normal weight	18.5-24.9
Overweight	25-29.9
Obesity Grade I	30-34.9
Grade II	35-39.9
Grade III	40+

A specific problem of MS and diabetes in general is the peripheral insulin resistance (IR), which is defined as genetically determined reduction of the receptors of peripheral cells and structural changes of the remaining receptors. This causes a decrease of the activity of intracellular phosphatidylinositol-3-kinase and therefore a reduction of glucose carrier molecules

in fat and muscle cells. In endothelial cells this kinase causes a disorder of NO secretion and by this it induces a peripheral vasoconstriction. Consequently, IR should be interpreted as an independent risk factor for vascular diseases [5, 11]. In early stages of the disease there is a compensatory increase of insulin secretion. But later there will be a dysfunction of the pancreatic beta cells. Then the catalytic capacity is limited and then an increase of proinsulin may be measured in the peripheral blood [3]. The portion of unprocessed proinsulin will increase more and more while the concentration of active insulin decreases [12].

Proinsulin will be disintegrated to proinsulin like molecules (PLMs) in the plasma by proteases [13, 14]. One of these PLMs is des-31,32-proinsulin. Increased plasma concentrations of this substance indicate functionally disintegrated beta cells, especially by chronically overstimulation of the insulin secretion. This may be the consequence of an insufficient therapy of a diabetic patient, but also when substances were administered which stimulate insulin secretion like sulfonylurea [15, 16].

Apart from genetic factors diabetes is mainly determined by adipositas and inactivity. Consequently weight reduction and activity (aerobic training) should be integral parts of any therapeutic concept [1, 2, 17]. This increases norepinephrine, epinephrine, and glucagons levels as well as those of glucose carrier molecules (GLUT-4) – all of them resulting in an increase of glucose uptake of the muscle cells and an increase of glycogen production in these cells. This could be shown in several studies: HbA1c, insulin resistance, body mass index (BMI), blood pressure, total cholesterol and LDL cholesterol, triglycerides were reduced as it was the 10 years risk for CHD [3]. Since it is difficult to measure insulin resistance directly e.g. by i.v. glucose tolerance or hyperglycaemic clamp test, the HOMA score may be the most often used system to detect (and to quantify) insulin resistance (fasting glucose x fasting insulin/22.5; values >2.0 indicate insulin resistance) [18]. But there is a disadvantage since the results are only reliable when no intact proinsulin was released to the plasma, which needs intact beta cells. A newer procedure is the direct measurement of proinsulin. In the IRIS-II study this was proven to have a specificity of 93% and a sensitivity of 47% compared to HOMA score [19, 20]. Others reported a specificity up to 100% and a sensitivity up to 53% (survey in [19]).

The study presented here was aimed to check changes of proinsulin levels in patients with MS with non-insulin dependent diabetes who performed an individual dietary and sports therapeutic programme. In contrast to others the program investigated here includes a significant amount of strength training, because it was assumed that this increases muscle mass and therefore the total mass of metabolically highly active tissue. The hypothesis of such training is that this metabolism supports the other factors of the therapeutic concept which cause weight loss. Studies have proven that any sport which includes strength training is of benefit also for patients or old persons and adverse reactions are minimal if the level of such training is carefully adjusted to the abilities of the individual (survey in [21]).

Methods

Participants

11 men and 11 women joined the study and performed an individual sport therapeutic programme and dietary education for three months. Inclusion criteria were MS (BMI of at least 27 kg/m^2) with non-insulin dependent diabetes and an age of at least 18 years. Exclusion criteria were any disease which would have excluded the patients from the training program, pregnancy, an age of less than 18 years and persons who were mentally unable to understand the study and to give an accurate written consent.

Procedure

Blood samples for proinsulin, HbA1c, and plasma glucose were taken at the beginning and after three months. All samples were taken at the same daytime (6 p.m.) and the volunteers were advised not to eat or drink anything (except water) for four hours prior to the blood sampling. BMI and body fat were also taken at the beginning and at the end of the three months period, the latter by impedance technology (Body Fat Monitor BF 306, Omron Healthcare Europe B.V., Hoofddorp/Netherlands).

All participants got detailed training and information in optimal nutrition and changes of lifestyle necessary to fight MS in standardized lectures at the beginning of the study. This and the coaching of the probands during the study was performed by a team consisting of a nutritionist, a diabetologist, a physician specialized in nutrition, and an educationalist. Together with the individuals the team analysed the nutrition of the participants in detail and an individual nutrition concept was then developed according to the recommendations of the German Society for Nutrition. For this process the software of the society was used ("DGHE Ernährungssoftware DGE-PC professional Version 3.0"). All probands had to take care for detailed documentation of their nutrition, body weight and participation in the sports program. Previous pilot studies had shown that this procedure increases the compliance of the patients significantly.

The individualized sport program used group dynamics to get the feeling of pleasure since obese persons are known to suffer from compunction because of their weight and that they are uninhibited in a group

Fig. 1. *Shoulder fixator for back muscle training*

Fig. 2. *Rudder traction machine for back muscle training*

Fig. 5. *Leg extensor system*

Fig. 3. *Latissimus dorsi trainer*

Fig. 4. *Pectoral muscle training*

Fig. 6. *Training System for the adductors and abductors of the hip*

Fig. 7. *Training system for the leg's extensor and flexor muscles*

of similar patients. Sports consisted of endurance and of strength training (2/3 to 1/3 of the time). Endurance training was performed in steady state modus for 30 (-60) min. in 1 (-2) units and with a pause of 30 min., when 2 units had to be done. The probands were allowed to choose between treadmills, spinning ergometers, or cross trainers to perform the training (all of them from Proxomed® Medizintechnik GmbH, Alzenau/Germany). The apparatuses used are computer assisted and they automatically reduce workload if a proband exceeds his or hers individual threshold.

The workload was strictly within aerobic range at 40 (-70)% of the individual maximal workload. This was tested by the IPN Test according to Lagerstrom et al. [22, 23]. This test evaluates the aerobic workload in W/kg body weight at the Mader threshold [24-27]. For higher accuracy the test does not follow the Hollmann scheme of ergometry [25] since it increases the workload at the cycle ergometer for 25 Watts every 2 minutes. All patients were tested in the presence of a physician. Heart rate during training (HRT) was evaluated as follows: $HRT = HR_{rest} + [(220\text{-age [yr]}) - HR_{rest}]^{*}X$ with X = workload during training in % of maximum workload. To control workload during training by heart rate (HR) is generally accepted as safe and effective since decades and widely used in any kind of endurance sports, also with patients (e.g. [25, 28]).

Strength training was performed as extensive interval strength endurance training (3x30 repetitions without load relieving and 1 min. pause between the three sets). For back muscle training the so-called "shoulder fixator" (Fig. 1), the rudder traction machine (Fig. 2), and Latissimus-dorsi-trainer (Fig. 3) were used. For pectoral muscle training the pectoral system as shown in Fig. 4 was used. Shoulder muscles were trained with dumb-bells: with the elbow flexed at 90° the arms had to be lifted laterally until the elbows were at the shoulder's level. Arms were trained with biceps curls and triceps extension and the legs with the leg extensor (Fig. 5). The systems for the adductors and abductors of the hip and those for the leg's flexors are shown in Fig. 6 and Fig. 7, respectively.

Training was not allowed before detailed information was given about correct body position, how to move and to breathe. The probands were advised to avoid forced respiration during expulsion strictly. Any training was surveyed by trainers and a sport physician. Every six weeks the loads of the strength training was regularly adjusted to the actual training status to keep the load at 40-60% of he maximum force as it was done for the endurance training.

Statistical analysis

Because some data did not follow normal distribution non-parametric tests were used for statistics (Wilcoxon-signed-rank-Test). $P < 0.05$ was defined as significant. The ethical commission of the University of Salzburg fully agreed with the study design.

Results

Primary outcome measures concerned proinsulin, secondary ones were HbA1c, plasma glucose concentration, and BMI.

Before the training was started, mean proinsulin levels were 22.88 pmol/l (+/-18.58; median: 16.1; range: 7.2 – 67.1). Three months later the respective values were 20.45 pmol/l (+/-22.12; median: 10.9; range 3.4 – 86.2). Caused by the large statistical spread of the data the difference showed a trend towards lower

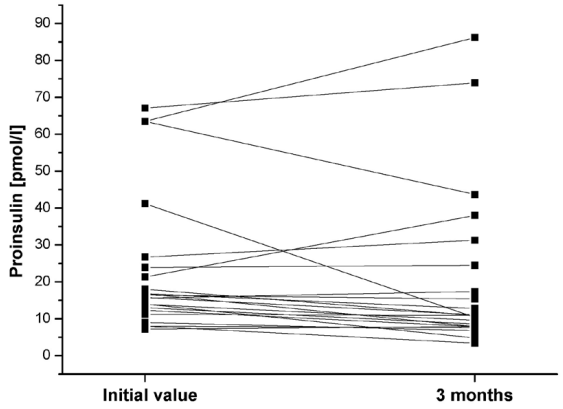

Fig. 8. *Individual changes of proinsulin concentrations (values before and after the three months training period; whole study group P=0,12)*

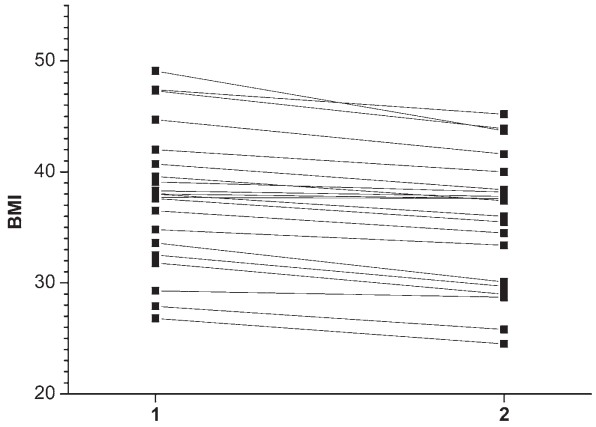

Fig. 10. *Individual changes of BMI (1: values before, 2: values after the three months of training period)*

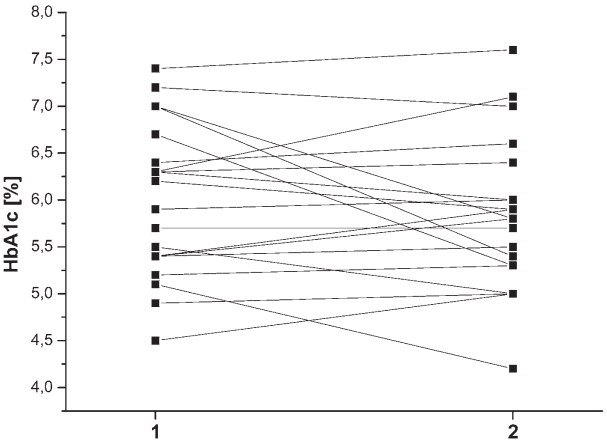

Fig. 9. *Individual changes of HbA1c (1: values before, 2: values after the three months training period)*

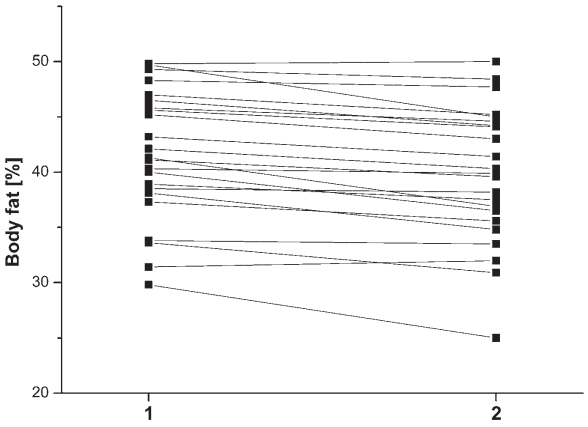

Fig. 11. *Individual changes of body fat [%] (1: values before, 2: values after the three months of training period)*

proinsulin levels, but the difference of -2.43 pmol/l was not significant (P = 0.12). A detailed analysis of the data was performed to get more information about the statistical spread and the occurrence of non-responders. While most volunteers (n=16) showed a more or less pronounced decrease of proinsulin a minority of 6 persons showed an increase (Fig 8). This increase was independent from the other factors investigated and it is unlikely that these probands did not follow the training plan or dietary restrictions since BMI (weight loss), HbA1c, and plasma glucose were according to the results of the rest of the collective.

When the proinsulin data were analysed after grouping them according to drug intake (11 persons without medication, 7 persons with metformin; 4 persons where drug intake was unclear or had been changed by the family physician during the study were excluded from this analysis) there was a tendency (P = 0.7) to lower values in the group without medication, but a significant reduction of proinsulin levels in the group which took metformin during the whole observation period (P = 0.02).

Mean HbA1c was 6.06% (+/-0.82; median 6.25; range 4.5 – 7.4) at the beginning and 5.91% (+/-4.2; median 5.85; range 4.2 – 7.6) at the end of the study (Fig 9). The difference of -0.15% is not significant. When the probands are grouped as described above the difference is not significant in those who do not take metformin (P = 0.69), but marginal significant in the metformin group (P = 0.05).

Body weight decreased from 104.6kg (+/-23.6) to 99.6 kg (+/-22.7) (P < 0.001). With a mean of 5 kg the decrease was slightly more pronounced in women than in men (4 kg, n.s.). BMI was reduced significantly during the study (-2.1 kg/m^2; P < 0.001, Fig 10). While it was 37.75 (mean) at the beginning of the study (+/-6.22; median 38.0; range 26.8 – 49.1) it was 35.65 (mean) at the end (+/-5.89; median 37.4; range 24.5 – 45.2). Except of two persons who showed a constant body weight all probands showed a decrease of BMI, some of them for more than 3 kg/m^2. Considering the WHO criteria for obesity [29] 6 persons reduced their obesity class for one class (one person reached normal weight). No person showed an increase in body mass. A comparison of the subgroups with or without metformin medication showed a significant reduction of BMI in both subgroups, although it is less pronounced in the metformin group (P = 0.001 and

$P = 0.03$). Body fat of the study group was 40.4% (+/-5.84) at the beginning and 38.3% (+/-6.46; $P < 0.001$) at the end of the study (Fig 11).

Discussion

We investigated the effect of a sport therapeutic program which combined aerobic endurance training, strength training, and dietary education on proinsulin levels, BMI, and HbA1c. While there was a remarkable reduction in body weight or BMI during the relatively short observation period of only three months, proinsulin levels showed a tendency to lover concentrations only, as it was also found for HbA1c.

First of all the study has proven, that the sport therapeutic programme which combines sport, dietary training and individual coaching, is effective since all probands showed a significant reduction of their body weight. According to the WHO classification of obesity [29] 6 persons reduced their risk class by one and one person showed normal BMI at the end of the study. There is general consensus that this reduces the risk for cardiocirculatory diseases [8]. Although we did not measure abdominal circumference which represents abdominal fat as an independent risk factor for cardiocirculatory diseases as well as for several other diseases, there is no doubt that the remarkable weight reduction of our probands also included abdominal fat [1, 8, 17, 30-44].

Since muscular tissue is heavier than fat and the training programme aimed to increase the metabolic highly active muscle tissue the reduction of fat during the observation period is higher than the data of the body weight indicate. This is confirmed by the highly significant decrease of % body fat in all participants. Studies which include fat-free muscle mass as parameter are rare, which is surprising since muscles are metabolically highly active tissue [17]. Garrow et al. reported, that strength training did not induce a significant loss of body weight, but an increase of fat-free muscle mass [45]. Waddel et al. reported similar results for an observation period of 40 weeks [46]. In contrast to these studies all of our subjects showed booth, loss of total weight loss (respectively body mass) and an increase of muscle mass. But a direct comparison is difficult as the protocols were different. As reported by Liu strength training was safe since no participant complained any kind of muscular problems during the study period [21].

The main interest of our study was to get information about changes of proinsulin and IR during the sport program. IR can be found in many individuals, especially when they are obese, without a diabetes may be clinically diagnosed. These people are able to compensate the increased demand of insulin. Later, about 1/3 of these persons show an impaired function of the pancreatic beta cells and this is the onset of a clinically relevant diabetes [14]. Studies have shown that micro- and macrovascular damage may start at a very early stage of the disease [14, 47, 48]. This highlights the importance to fight IR as early and as consequently as possible.

Since traditional risk classifications of diabetic patients by HbA1c, serum glucose, lipids, BMI, and blood pressure consider symptoms only and the predictive value of such a procedure is limited because the primary dysfunction, IR or beta cell dysfunction, cannot be identified, procedures which enable a more detailed analysis could be of benefit for therapy [49]. Therefore Pfützner et al. suggest to differentiate patients who show insulin sensitivity and normal insulin secretion, but a dysfunction of the early stage of insulin secretion ("class I") from others, who show an increasing IR but an increased insulin secretion of the beta cells ("class II"). In "class IIIa" the catalytic capacity is at its limits and the concentration of intact proinsulin increases. This leads to the final stage IIIb which is characterised by a total depletion of beta cell secretion. Patients at stages I and II should have the greatest benefit from any procedure which charges insulin secretion and decreases IR, e.g. by sport [3]. There is some evidence that females may have a higher benefit than males by activity or sports [50]. But this may be balanced by a gender-specific training with males at higher intensity and females at lower intensity but for a significantly longer duration of the respective training [50-54]. But such differences may be biased, because women are significantly less active in sports than men [55, 56] and individuals tend to overestimate their level of activity [57].

The training of muscles is of special interest to fight IR. With the increase of muscle mass there is an increase of basal metabolic rate [58]. Some studies showed that the combination of aerobic endurance and strength training ameliorate the metabolic situation and reduce the risk of complications which are associated with diabetes (survey in [59, 60]). A risk reduction for 20 to 70% to develop diabetes is possible, but the highest reduction was shown in all study groups when different training techniques were combined with other procedures (dietary weight loss etc.) (survey in [61, 62]).

In our study there was a significant effect of the decrease of proinsulin concentrations in patients who were also treated by metformin. This may be a consequence of the limited size of the study group. But this may also be a consequence of the drug's effect on the glucose metabolism. Since our patients were not at diabetes stage IIIb according to Pfützner as mentioned above, a reduced enteral glucose resorption, an inhibition of the hepatic gluconeogenesis and an increase of the muscle's glucose uptake – all of which induced by metformin – cause a minor activity of the beta cells while the catalytic activity is not at its limit. As a consequence there is less proinsulin in the serum.

Our study has some limitations. The effect of metformin was already discussed above. We compared persons with or without such a medication, but since the size of the subgroups is limited this should be interpreted as pilot study only. The limited duration may have reduced the effect of changes in HbA1c since this is directly correlated to the lifespan of erythrocytes which is approximately 90 days. Another problem was that there might be a bias by the selection of the patients. Since diabetic persons as well as their physicians regularly underestimate the cardiac risk of such a patient [63] we had to take care for ethical reasons that the risk for our participants was minimal since this kind of training was not investigated before. With the data available now another study should be planned to evaluate whether there are specific diagnoses like cardiovascular diseases where the patients have more or less benefit of such training. Some hormones like adiponectin are of specific influence on the insulin sensitivity [64, 65]. Such tests and those of high sensitive C-reactive protein (hsCRP) may be also included in further studies. Due to logistical problems it was not always possible to get blood samples for glucose and proinsulin before breakfast. This may have caused some of the variance of the data. Another factor is the interindividual variability of proinsulin. This problem may be solved by a larger size of the study group. Based on the data of the study presented here, a study group to investigate the effect on proinsulin with a power of 80% should include 156 participants and to evaluate HbA1c 140 persons would be necessary. We provided a close cooperation of the participants and the personnel also concerning dietary topics. But for practical reasons we did not control any food intake. Since some food ingredients were discussed as being a determining factor of MS the aspects of nutrition may be focused more in the next study. At least vitamin D uptake should be monitored since it this substance may be an important predictor of hsCRP, plasma glucose, and systemic inflammation – all of which are closely related to MS [66]. Our study cannot prove the long-term effect on our patients. Therefore a follow-up with re-evaluation after one and two years is necessary [67]. In contrast to others who did not get any effect after a period of 14 days, our training was an adequate stimulus, both the duration and the intensity [68]. However, it is not yet known which the optimal intensity of strength training for patients with MS might be and how often per week such training should be performed to gain the best possible effect.

However, although the effect of decrease of body mass may be partially camouflaged because there was an increase of muscle mass which is heavier than fat, the concept has been proven to be an effective strategy to decrease several risk factors on metabolic syndrome. Because there is some bias between dietary procedure and training we cannot define in detail which of both was the major effect. But since the primary goal of our pilot study was to investigate the combination of both, it was not intended to analyze both factors separately. Further investigations are necessary to detect subgroups of patients who may have the optimal benefit and more data are necessary to establish an optimized structure of the training for the patients. Such studies should cover longer observation periods (6 months or more) and should also have a follow-up study after about 1-3 years.

Acknowledgements

The authors would like to thank Mr. F. Neuroth and the whole team of "Go21" for their assistance while we performed the study. Prof. Dr. R.-D. Hilgers and his team at the Institute of Medical Statistics, RWTH Aachen University, for their careful advice, and Mrs. Neif, Mrs. Paul, and Mrs. Rohrmann to assist us in laboratory analyses and nutrition program.

Declaration of interest

The authors report no conflicts of interest.

References

1. Eckert K. Impact of physical activity and bodyweight on health-related quality of life in people with type 2 diabetes. DMSOTT 2012; 5: 303-11.
2. Halle M, Kemmer F-W, Stumvoll M, et al. Körperliche Aktivität und Diabetes mellitus - Evidenzbasierte Leitlinie der Deutschen Diabetes-Gesellschaft. 2008 [cited; Available from: http://www.awmf.org/uploads/tx_szleitlinien/057-022_S3_Koerperliche_Aktivitaet_und_Diabetes_mellitus_10-2008_10-2013.pdf.
3. Pfutzner A, Forst T. Insulinresistenz und Dysfunktion der Betazellen früher erkennen-Können Typ 2-Diabetiker noch gezielter behandelt werden? Practical diagnosis in insulin resistance and beta-cell dysfunction and resulting therapeutic consequences. *Fortschr Med* 2004; 146(20): 32-3, 35.
4. Stamler J, Vaccaro O, Neaton JD, et al. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; 16(2): 434-44.
5. Wilhelm B, Pfützner A, Forst T. Metabolische Störungen bei kardiovaskulären Risikopatienten. *Diabetes Stoffw Herz* 2006; 15(3): 59-66.
6. Juutilainen A, Lehto S, Ronnemaa T, et al. Type 2 diabetes as a "coronary heart disease equivalent": an 18-year prospective population-based study in Finnish subjects. *Diabetes Care* 2005; 28(12): 2901-7.
7. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; 339(4): 229-34.
8. Wormser D, Kaptoge S, Di Angelantonio E, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet 377* 2011; 377: 1085-95.
9. Farrer M, Fulcher G, Albers CJ, et al. Patients undergoing coronary artery bypass graft surgery are at high risk of impaired glucose tolerance and diabetes mellitus during the first postoperative year. *Metabolism* 1995; 44(8): 1016-27.
10. Fujiwara R, Kutsumi Y, Hayashi T, et al. Relation of angiographically defined coronary artery disease and plasma concentrations of insulin, lipid, and apolipoprotein in normolipidemic subjects with varying degrees of glucose tolerance. *Am J Cardiol* 1995; 75(2): 122-6.

11. Zeng G, Nystrom FH, Ravichandran LV, et al. Roles for insulin receptor, PI3-kinase, and Akt in insulin-signaling pathways related to production of nitric oxide in human vascular endothelial cells. *Circulation* 2000; 101(13): 1539-45.
12. Blickle JF, Sapin R, Andres E. Contribution of total and intact proinsulins to hyperinsulinism in subjects with obesity, impaired glucose tolerance or type 2 diabetes. *Diabetes Metab* 2000; 26(4): 274-80.
13. Galloway JA, Hooper SA, Spradlin CT, et al. Biosynthetic human proinsulin. Review of chemistry, in vitro and in vivo receptor binding, animal and human pharmacology studies, and clinical trial experience. *Diabetes Care* 1992; 15(5): 666-92.
14. Pfutzner A, Forsst T. Intaktes Proinsulin als kardiovaskulärer Risikofaktor und prädiktiver diagnostischer Marker für die Insulinresistenz bei Patienten mit Diabetes mellitus Typ 2. *Diab Stoffw* 2004; 14: 193-200.
15. Panahloo A, Mohamed-Ali V, Andres C, et al. Effect of insulin versus sulfonylurea therapy on cardiovascular risk factors and fibrinolysis in type II diabetes. *Metabolism* 1998; 47(6): 637-43.
16. Hermann LS, Ranstam J, Vaaler S, et al. Effects of antihyperglycaemic therapies on proinsulin and relation between proinsulin and cardiovascular risk factors in type 2 diabetes. *Diabetes Obes Metab* 1999; 1(4): 227-32.
17. Luley C, Blaik A, Westphal S. Nachhaltige Gewichtsreduktion. *Dt Ärztebl* 2011; 108(30): A1642.
18. Pfutzner A, Marx N, Lubben G, et al. Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control: results from the pioneer study. *J Am Coll Cardiol* 2005; 45(12): 1925-31.
19. Pfützner A, Standl E, Hohberg C, et al. IRIS II Study: Intact Proinsulin is Confirmed as Highly Specific Marker for Insulin Resistance in a Cross-Sectional Study Design. *Diab Technol Ther* 2005; 7: 478-86.
20. Pfutzner A, Pfutzner AH, Kann PH, et al. Clinical and laboratory evaluation of a new specific ELISA for intact proinsulin. *Clin Lab* 2005; 51(5-6): 243-9.
21. Liu CJ, Latham N. Adverse events reported in progressive resistance strength training trials in older adults: 2 sides of a coin. *Arch Phys Med Rehabil* 2010; 91(9): 1471-3.
22. Lagerstrøm D, Froböse I, Konrad P, et al. Ein Zwei- und Vierstufen-Screening-Test am Fahrradergometer. Eine experimentelle Studie. [A two and four level screening test with the cycle ergometer. An experimental study]. *Gesundheitssport Sporttherapie* 1990; 6(4): 10-12.
23. Lagerstrøm D, Trunz E. IPN-Ausdauertest für den Fitness- und Gesundheitssport. *Gesundheitssport Sporttherapie* 1997; 13(2): 68-71.
24. Mader A, Heck H. A theory of the metabolic origin of "anaerobic threshold". *Int J Sports Med* 1986; 7(1): 45-65.
25. Hollmann W, Hettinger T. Sportmedizin, Grundlagen für Arbeit, Training und Präventivmedizin. Stuttgart: Schattauer, 2000.
26. Heitkamp HC, Holdt M, Scheib K. The reproducibility of the 4 mmol/l lactate threshold in trained and untrained women. *Int J Sports Med* 1991; 12(4): 363-8.
27. McGehee JC, Tanner CJ, Houmard JA. A comparison of methods for estimating the lactate threshold. *J Strength Cond Res* 2005; 19(3): 553-8.
28. Zeni AI, Hoffman MD, Clifford PS. Energy expenditure with indoor exercise machines. Jama 1996; 275(18): 1424-7
29. Puska P, Nishida C, Porter D. Obesity and overweight. World Health Organization http://www.who.int/dietphysicalactivity/media/en/gsfs_obesity.pdf 2003
30. N.N. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet 2011; 377: 1085–95.
31. Silber S, Richartz B, Bischoff B, et al. Erhöhter Bauchumfang als kardiovaskulärer Risikofaktor in Deutschland: Ergebnisse an über 55000 Patienten (Abstract). *Clin Res Cardiol* 2006; 95.
32. Anderssen SA, Holme I, Urdal P, et al. Associations between central obesity and indexes of hemostatic, carbohydrate and lipid metabolism. Results of a 1-year intervention from the Oslo Diet and Exercise Study. *Scand J Med Sci Sports* 1998; 8(2): 109-15.
33. Bjorntorp P. The associations between obesity, adipose tissue distribution and disease. *Acta Med Scand Suppl* 1988; 723: 121-34.
34. Choi SY, Kim D, Oh BH, et al. General and abdominal obesity and abdominal visceral fat accumulation associated with coronary artery calcification in Korean men. *Atherosclerosis* 2010; 213(1): 273-8.
35. Cignarelli M, DePergola G, Picca G, et al. Relationship of obesity and body fat distribution with ceruloplasmin serum levels. *Int J Obes Relat Metab Disord* 1996; 20(9): 809-13.
36. Da Silva JL, Barbosa DS, de Oliveira JA, et al. Centripetal distribution of body fat, overweight and cardiorespiratory fitness: association with insulin sensitivity and metabolic alterations. *Arq Bras Endocrinol Metabol* 2006; 50(6): 1034-40.
37. Ekblom-Bak E, Hellenius ML, Ekblom O, et al. Fitness and abdominal obesity are independently associated with cardiovascular risk. *J Intern Med* 2009; 266(6): 547-57.
38. Fox KA, Despres JP, Richard AJ, et al. Does abdominal obesity have a similar impact on cardiovascular disease and diabetes? A study of 91,246 ambulant patients in 27 European countries. *Eur Heart J* 2009; 30(24): 3055-63.
39. Giugliano G, Brevetti G, Laurenzano E, et al. The prognostic impact of general and abdominal obesity in peripheral arterial disease. *Int J Obes (Lond)*; 34(2): 280-6.
40. Golledge J, Clancy P, Jamrozik K, et al. Obesity, adipokines, and abdominal aortic aneurysm: Health in Men study. *Circulation* 2007; 116(20): 2275-9.
41. Iglesias Bolanos P, Olivar Roldan J, Penalver Talavera D, et al. Effect of abdominal obesity on size of myocardial infarction. *Endocrinol Nutr* 2009; 56(1): 4-8.
42. Lear SA, Humphries KH, Kohli S, et al. Visceral adipose tissue, a potential risk factor for carotid atherosclerosis: results of the Multicultural Community Health Assessment Trial (M-CHAT). *Stroke* 2007; 38(9): 2422-9.
43. Mahabadi AA, Massaro JM, Rosito GA, et al. Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham Heart Study. *Eur Heart J* 2009; 30(7): 850-6.
44. Peverill RE, Teede HJ, Malan E, et al. Relationship of waist and hip circumference with coagulation and fibrinolysis in postmenopausal women. *Clin Sci (Lond)* 2007; 113(9): 383-91.
45. Garrow JS, Summerbell CD. Meta-analysis: effect of exercise, with or without dieting, on the body composition of overweight subjects. *Eur J Clin Nutr* 1995; 49(1): 1-10.
46. Wadden TA, Vogt RA, Andersen RE, et al. Exercise in the treatment of obesity: effects of four interventions on body composition, resting energy expenditure, appetite, and mood. *J Consult Clin Psychol* 1997; 65(2): 269-77.
47. Reaven GM, Chen YD, Hollenbeck CB, et al. Plasma insulin, C-peptide, and proinsulin concentrations in obese and nonobese individuals with varying degrees of glucose tolerance. *J Clin Endocrinol Metab* 1993; 76(1): 44-8.
48. Haffner SM, Mykkanen L, Stern MP, et al. Relationship of proinsulin and insulin to cardiovascular risk factors in nondiabetic subjects. *Diabetes* 1993; 42(9): 1297-302.
49. Pfutzner A, Weber MM, Forst T. Biomarkers for Assessing Beta-Cell Function and Insulin Resistance in Type 2 Diabetes. *Diabetes, Stoffwechsel und Herz* 2008(1): 37-41.
50. Bucksch J, Schlicht W. Reduziert sich das Mortalitätsrisiko sowohl für normal- als auch für übergewichtige Personen durch körperliche Aktivität? *Dt Ztschr Sportmed* 2010; 61(3): 72-8.
51. Bucksch J. Physical activity of moderate intensity in leisure time and the risk of all cause mortality. *Br J Sports Med* 2005; 39(9): 632-8.
52. Lee IM. No pain, no gain? Thoughts on the Caerphilly study. *Br J Sports Med* 2004; 38(1): 4-5.

53. Morris JN, Clayton DG, Everitt MG, et al. Exercise in leisure time: coronary attack and death rates. *Br Heart J* 1990; 63(6): 325-34.
54. Oguma Y, Shinoda-Tagawa T. Physical activity decreases cardiovascular disease risk in women: review and meta-analysis. *Am J Prev Med* 2004; 26(5): 407-18.
55. Varo JJ, Martinez-Gonzalez MA, De Irala-Estevez J, et al. Distribution and determinants of sedentary lifestyles in the European Union. *Int J Epidemiol* 2003; 32(1): 138-46.
56. Leyk D, Rüther T, Wunderlich M, et al. Sportaktivität, Übergewichtsprävalenz und Risikofaktoren. *Dt Ärztebl* 2008; 105(46): 793-800.
57. Walsh MC, Hunter GR, Sirikul B, et al. Comparison of self-reported with objectively assessed energy expenditure in black and white women before and after weight loss. *Am J Clin Nutr* 2004; 79(6): 1013-9.
58. Yates T, Khunti K, Bull F, et al. The role of physical activity in the management of impaired glucose tolerance: a systematic review. *Diabetologia* 2007; 50(6): 1116-26.
59. Kirk AF, Barnett J, Mutrie N. Physical activity consultation for people with Type 2 diabetes: evidence and guidelines. *Diabet Med* 2007; 24(8): 809-16.
60. Ostergard T, Jessen N, Schmitz O, et al. The effect of exercise, training, and inactivity on insulin sensitivity in diabetics and their relatives: what is new? *Appl Physiol Nutr Metab* 2007; 32(3): 541-8.
61. Kujala UM. Evidence for exercise therapy in the treatment of chronic disease based on at least three randomized controlled trials--summary of published systematic reviews. *Scand J Med Sci Sports* 2004; 14(6): 339-45.
62. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *Cmaj* 2006; 174(6): 801-9.
63. Hohberg C, Lübben G, Forst T, et al. Kardiovaskuläres Risiko bei Diabetes mellitus Typ 2. *Diabetes Stoffwechsel und Herz* 2007; 3: 173-7.
64. Trujillo ME, Scherer PE. Adiponectin - journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. *J Intern Med* 2005; 257(2): 167-75.
65. Rolland C, Hession M, Broom I. Effect of weight loss on adipokine levels in obese patients. *DMSOTT* 2011; 4: 315–23.
66. Salekzamani S, Neyestani TR, Alavi-Majd H, et al. Is vitamin D status a determing factor for metabolic syndrome? A case-control study. *DMSOTT* 2011; 4: 205-12.
67. Frey I, Dapp N, König D, et al. Weight Management through M.O.B.I.L.I.S., an exercise based weight loss program: 2-year results. *Dt Ztschr Sportmed* 2010; 61(1): 19-22.
68. Brinkmann C, Geisler S, Klemme F, et al. Effects of strength training on the metabolic syndrome - relevance of changes in muscle morphology. *Dt Ztschr Sportmed* 2009; 60(12): 394-8.

Accepted: November 30, 2012
Published: December 21, 2012

Address for correspondence:
Thomas Küpper, Prof., MD, PhD
Institute for Occupational and Social Medicine
RWTH Aachen University Pauwelstr. 30
D-52074 Aachen
Email: tkuepper@ukaachen.de

Sarah Müller: Sarah.mueller@rwth-Aachen.de
Victoria Jacobson: Victoria.jakobson@rwth-Aachen.de
Michael Müller: Mueller.rohrmann@t-online.de
Carolin Westphal: Carolin.westphal@rwth-Aachen.de