EFFECTS OF A 9 MONTHS EXERCISE TRAINING ON INFLAMMATORY AND LIPID MARKERS IN TYPE 2 DIABETIC PATIENTS

Antina Schulze DDS & Martin Busse MD, PHD

General Outpatient Ambulance and Sports Dentistry of the Institute of Sports Medicine, University of Leipzig, Germany

Abstract

Aims: Desired effects of a rehabilitative training are: Decreases in inflammation and lipid risk factors, in HbA1c, and increases in cardiopulmonary capacity. Though the beneficial effects of intense training are well established, no epidemiologic relevance of such training regimens has been found. Apparently a moderate and stress free program is an important prerequisite for lasting acceptance and life style change. Therefore studies should point to low but still effective training intensity. **Methods:** 33 type 2 diabetes patients (63.8 ± 6.9 years) with insulin regimen had a 9 months rehabilitative exercise training two times/week. Plasma levels of inflammatory and lipid markers, specific diabetic and training parameters were measured at baseline, after three, six and nine months.

Results: Rehabilitative training resulted in a significant increase in tumor necrosis factor-alpha (12.27 ± 7.93 vs. 15.12 ± 9.58 or 14.89 ± 9.25 $pgxl^{-1}$ after 6 or 9 months). Interleukin-6 was reduced significantly after 3 months (4.3 ± 7.02 vs. 3.92 ± 6.68 $pgxl^{-1}$) whereas C-reactive protein remained unchanged. Lipid parameters decreased markedly after 9 months (triglycerides 2.10 ± 1.2 vs. 1.82 ± 1.07 $mmolxl^{-1}$; cholesterol 5.18 ± 1.12 vs. 4.92 ± 0.91 $mmolxl^{-1}$; LDL 3.24 ± 0.85 vs. 2.88 ± 0.66 $mmolxl^{-1}$). HDL and HbA_{1c} remained almost unchanged. Weight decreased moderately but significantly (99.21 ± 17.62 vs. 97.73 ± 16.61 kg) also BMI (35.28 ± 5.3 vs. 34.78 ± 5.34). Endurance capacity was increased by 103%, rate-pressure product at rest and blood pressure markedly decreased.

Conclusions: 9 months of rehabilitative exercise training in type 2 diabetes patients had moderate but significant effects on lipid factors, no relevant effect on C-reactive protein and Interleukin-6 but resulted in a marked increase in tumor necrosis factor-alpha. A marked improvement in endurance capacity, cardiac stress and blood pressure was seen.

Key words: Exercise, diabetes mellitus, immune markers, risk factors, physical endurance

Abbreviations: BG= blood glucose, EC= endurance capacity, RPP= rate-pressure product

1. INTRODUCTION

It is recognized that the path from physical inactivity and obesity to lifestyle-related diseases involves low-grade inflammation, indicated by elevated plasma levels of inflammatory markers. Systemic and local inflammation is hypothesized to play a significant role in the pathogenesis and progression of insulin resistance, impaired glucose tolerance and even diabetes resulting from chronic activation of the innate immune system. In obesity, the white adipose tissue is characterized by an increased production and secretion of inflammatory molecules including TNF-α and interleukin-6 (IL-6), which have local and also systemic effects on other organs. Recent data indicate that white adipose tissue is infiltrated by macrophages, which may be a major source of locally-produced pro-inflammatory cytokines such as TNF-α and IL-6 [1]. Increased macrophage infiltration of adipose tissue has been described in obese individuals, as well as an increase in "classically activated" macrophages [2].

Obesity and type 2 diabetes mellitus are associated with many metabolic disorders including dyslipidemia, hypertension and artheriosclerosis [3].

C-reactive protein (CRP) levels are directly related to increased risk of coronary disease and diabetes and have been associated with both high body mass index (BMI) and low physical activity in cross sectional studies [4, 5, 6,7,8]. CRP is produced by the liver in response to an acute infection or inflammation. Elevated concentrations of CRP have been associated with coronary heart disease, obesity, diabetes, smoking, and sedentary lifestyle [9]. CRP levels, inversely related to cardiorespiratory fitness, are associated with an increased risk of cardiovascular disease. Numerous studies have observed an inverse association between CRP and regular physical activity and/ or exercise [4, 5, 6, 7, 8, 10]. In contrast few studies have prospectively examined the effect of exercise training alone on resting levels of CRP, particularly in individuals with elevated levels of CRP [11, 12].

Controversy about the role of TNF-alpha in insulin resistance has been raised by inconsistent results in human studies. Some find no association [12, 14] whereas others do [15, 16]. Other results suggest that exercise may induce increased levels of anti-inflammatory cytokines (e.g. IL-10, IL-6), and cytokine inhibitors (e.g. IL-1 receptor antagonist, TNF-α receptor) [17, 18].

Since diabetes is a chronic low-grade systemic inflammation, we suggest that exercise may have anti-inflammatory effects and improves the overall immune status of type 2 diabetic patients with insulin regimen.

2. METHODS

Study population and clinical data: 33 well-controlled type 2 diabetic subjects (17 females, 16 males, 63.8 ± 6.9 years, weight 99.21 ± 17.62 kg, height 167.6 ± 9.6 cm, BMI 35.28 ± 5.3) with insulin regimen participated in a 9 months combined endurance/resistance exercise training program. Control of diabetes was measured by the percentage of glycated hemoglobin in the blood (mean: 6.4 ± 0.76% (46.45 mmol/mol)). At baseline, after three, six and nine months, fasting blood samples for measurement of inflammatory and lipid markers were taken. 88 % of the Patients had an antihypertensive medication, 24 % were taking aspirin and 48 % drugs for lipid disorders. No health and nutrition intervention was conducted. There were no relevant changes in medication throughout the study period. No regular physical exercise was performed by any of the patients before the study, most of them were unemployed. Exclusion criteria were: acute/chronic infections, antibiotic therapy, rheumatoid diseases.

Laboratory measurements: Fasting blood samples were collected at baseline, after three, six and nine months. Laboratory analyses were performed at 8 h after a 12 h overnight fast. Concentrations of IL-6, TNF-alpha, and C-reactive protein were measured as well as the lipid profiles (triglycerides, cholesterol, high- and low-density lipoproteins (HDL, LDL)), leukocytes, thrombocytes, and the creatine kinase levels.

Training protocol: The patients exercised two times per week (A- and B- session). All A-Sessions commenced and concluded with a warming-up and cooling-down period. Session A consisted of 45 minutes endurance training (cycle-ergometer, tread mill, rowing-ergometer) and 15min of pulley exercises. Session B consisted of 45 minutes of supervised moderate swimming. The program started out with low intensity training for each form of exercise and was weekly increased according to the individuals' increasing endurance capacity. Before and after each exercise set heart rate, blood pressure, blood glucose, and work load were measured and recorded. Data at baseline and after 9 months of training were analysed. The cardiac load was estimated using the rate-pressure product, divided by 1000.

Statistical analyses: All data are presented as means ± SD. Pairwise comparisons were carried out using the Wilcoxon matched pairs signed rank test. A p-value <0.05 was considered to indicate significance, $p<0.01$ was accepted as very significant and $p<0.005$ as extremely significant.

3. RESULTS

Body composition and metabolic data

	baseline	**3 months**	**6 months**	**9 months**	**p-value (baseline vs. 3 months)**	**p-value (baseline vs. 6 months)**	**p-value (baseline vs. 9 months)**
weight (kg)	99.21±17.62	97.73±16.39	97.59±16.61	97.73±16.61	<0.001	<0.006	<0.006
BMI	35.28±5.3	34.79±5.18	34.74± 5.23	34.78±5.34	<0.0008	<0.004	<0.005
HbA_{1c} (%)	6.40±0.76	6.30±0.73	6.41±0.78	6.51±0.73	n.s.	n.s.	n.s.
IFCC (mmol/mol)	46.45	45.36	46.56	47.65	n.s.	n.s.	n.s.

Table 1. Weight, BMI, HbA_{1c}, IFCC and the significances between baseline vs. 3, 6, and 9 months of program participation.

Program effects:

There was a minor but significant and lasting decrease of body weight and BMI already after 3 months, but no relevant effect on HbA_{1c} and IFCC (Tab. 1).

Inflammatory markers

inflammatory markers	baseline	3 months	6 months	9 months	p-value (baseline vs. 3 months)	p-value (baseline vs. 6 months)	p-value (baseline vs. 9 months)
s-CRP(mgxl^{-1})	4.14±3.40	4.24±4.08	3.79±2.94	4.24±4.35	n.s.	n.s.	n.s.
IL-6 (pgxl^{-1})	4.30±7.02	3.92±6.68	3.95±6.53	3.98±6.74	<0.03	n.s.	n.s.
TNF-α (pgxl^{-1})	12.27±7.93	12.79±9.65	15.12±9.58	14.89±9.25	n.s.	<0.002	<0.001
thrombocytes (exp9xl^{-1})	242.84±62.60	235.03±60.32	245.7±59.96	237.88±63.71	n.s.	n.s.	<0,04
leucocytes (exp9xl^{-1})	6.75±1.53	6.75±1.50	6.82±1.37	6.77±1.43	n.s.	n.s.	n.s.
creatine kinase (IFCC, ukatxl^{-1})	2.76±2.12	2.65±2.12	2.35±1.47	2.32±1.31	n.s.	<0.03	<0.09

Table 2. s-CRP, IL-6, TNF-α, thrombocytes, leucocytes, and creatine kinase levels and the significances between baseline vs. 3, 6, and 9 months of program participation.

Baseline levels of CRP were below 5 mgxl^{-1} but markedly above 1 mgxl^{-1}. There was only a minor significant decrease of IL-6 after 3 months. The most striking result is a marked increase in TNF-α which was significant after 6 and 9 months. A significant decrease in thrombocytes and creatine kinase were measured after 9 and 6 months respectively. There was no relevant change in leucocytes (Tab. 2).

Lipid parameters

lipid parameters (mmolxl^{-1})	baseline	3 months	6 months	9 months	p-value (baseline vs. 3 months)	p-value (baseline vs. 6 months)	p-value (baseline vs. 9 months)
Triglycerides	2.10±1.20	1.89±1.25	1.96±1.18	1.82±1.07	n.s.	n.s.	<0.03
Cholesterol	5.18±1.12	4.93±1.16	5.12±1.17	4.92±0.91	n.s.	n.s.	<0.03
HDL	1.22±0.34	1.22±0.33	1.25±0.41	1.24±0.38	n.s.	n.s.	n.s.
LDL	3.24±0.85	2.99±0.75	3.11±0.83	2.88±0.66	n.s.	n.s.	<0.003

Table 3. Triglycerides, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) values and the significances between baseline vs. 3, 6, and 9 months of program participation.

Blood lipid risk parameters were all markedly decreased after 9 months, but there was no relevant change in HDL values (Tab. 3).

Cardio-circulatory parameters for resting conditions

	baseline	3 months	6 months	9 months	p-value (baseline vs. 3 months)	p-value (baseline vs. 6 months)	p-value (baseline vs. 9 months)
HR (beats x min^{-1})	77.61±12.26	74.09±12.29	75.97±12.48	73.03±8.53	<0.05	n.s.	<0.002

RR_{sys} **RR_{dia}** (mmHg)	142.42±19.18 81.64±11.18	138.76±18.75 83.30±11.46	134.06±15.94 78.09±11.21	135.64±17.01 76.73±9.78	n.s. n.s.	<0.02 n.s.	<0.04 <0.04
RPP ($HRxRR_{sys}$ $x1000^{-1}$)	11.03±2.11	10.28±2.28	10.17±1.93	9.98±1.78	<0.03	<0.03	<0.002

Table 4. HR= pre-exercise heart rate at rest, RR_{sys} and RR_{dia} = pre-exercise blood pressure systolic and diastolic at rest, and RPP= rate-pressure product before and after 3, 6, and 9 months of exercise training and the significances.

As a result of 6 and 9 months program participation blood pressure at rest was clinically significantly decreased. Since resting heart rate was also lower there was a marked effect on the resting rate-pressure product (Tab. 4).

Training effects on blood glucose before and after exercise

	baseline	**3 months**	**6 months**	**9 months**	**p-value (baseline vs. 3 months)**	**p-value (baseline vs. 6 months)**	**p-value (baseline vs. 9 months)**
BG pre ($mmolxl^{-1}$)	8.68±2.39	7.28±1.29	8.11±1.41	8.25±2.06	<0.006	n.s.	n.s.
BG post ($mmolxl^{-1}$)	6.17±1.67	5.21±1.03	5.63±1.60	5.65±1.50	<0.01	n.s.	n.s.
p value	<0.0001	<0.0001	<0.0001	<0.0001	n.s.	n.s.	n.s.

Table 5. Blood glucose (BG pre (-exercise), BG post (-exercise) ($mmolxl^{-1}$)) before and after exercise at baseline and after 3, 6, and 9 months of program participation. The significances between blood glucose levels before and after training sessions were given, and also the significances between baseline and after 3, 6 and 9 months.

There was an effect of the program on resting blood glucose and on the after training blood glucose after 3 months. In tendency these effects persisted after 6 and 9 months. Exercise always induced a marked decrease in blood glucose (Tab. 5).

Cardio-circulatory values immediately taken after cycle-ergometry

	baseline	**3 months**	**6 months**	**9 months**	**p-value (baseline vs. 3 months)**	**p-value (baseline vs. 3 months)**	**p-value (baseline vs. 3 months)**
EC (watt) **Increase** (%)	27.61±3.23	45.03±14.76	51.89±17.04	56.14±19.60	<0.0001 63	<0.0001 88	<0.0001 103
HR ($beatsxmin^{-1}$)	97.97±13.06	94.06±12.38	101.36±13.63	100.52±10.60	<0.02	n.s.	n.s.
RRsys **RRdia** (mmHg)	145.30±14.41 74.88±6.67	139.12±14.95 70.58±7.14	141.36±18.30 68.42±7.07	137.46±17.63 67.21±6.48	<0.02 <0.003	n.s. <0.0003	<0.01 <0.0001
RPP ($HRxRR_{sys}$ /1000)	14.31±2.63	13.11±2.4	14.42±3.09	13.89±2.79	<0.007	n.s.	n.s.

Table 6. EC= endurance capacity and increase of endurance capacity, HR= heart rate, RR_{sys} and RR_{dia}= post-exercise blood pressure systolic and diastolic, and RPP= rate-pressure product for exercise conditions before and after 3, 6, and 9 months of exercise. Please note that the rate-pressure product was similar although endurance capacity was increased at the different training time periods. It should also be noted that all values (except EC) do not refer to similar exercise values, but to the increased EC values.

As the most relevant exercise effect the rate-pressure product was decreased whereas training intensity was increased by 63 to 103 % of the initial values. In spite of increased exercise intensity also the diastolic pressure was very markedly and significantly decreased. The mean frequency of endurance/resistance training sessions in 9 months was 40.49 ± 9.69 or 13 times in a 3months period (Tab. 6).

4. Discussion

There are 3 major groups of effects to be discussed.

- Effects on inflammatory markers and cellular parameters
- Effects on lipid profile and blood glucose
- Effects on cardio-circulatory system and endurance capacity

Effects on immune parameters and inflammatory markers

TNF-α: most striking result of this study is a lasting significant increase of TNF-α.

Increased TNF-α following short or chronic training periods has been reported only twice (Table 7). In general there were no relevant changes or at times a decrease of TNF- α (Table 7). No such results in type 2 diabetes patients with insulin therapy have come to our knowledge.

Epidemiological studies and clinical interventions have reported contradictory findings related to dietary or exercise interventions and the resulting alterations in plasma cytokines [19]. Carey et al. [20] recently reported a lack of association between skeletal muscle TNF-α mRNA and circulating levels of TNF-α with whole-body insulin sensitivity in a wide variety of subjects including individuals with type 2 diabetes. Therefore, the role of TNF-α in the development of insulin resistance in humans is unclear and requires further research.

Various reported exercise and training effects on TNF-alpha, C-reactive protein, and Interleukin-6

author(s), year	type of exercise training	study population	TNF-α	CRP	IL-6
Loria-Kohen et al. (2013) [21]	22 weeks exercise training and caloric restriction (strength, endurance, combined)	84 obese	↓	↓	↓
Nikseresht et al. (2014) [22]	3 months nonlinear resistance + aerobic interval training	12 and 10 men middle aged and obese	n.s.	n.s.	n.s.
Donges et al. (2013) [23]	3 months exercise training (resistance/endurance)	47 untrained middle aged men	↓	n.s.	↓
Kim et al. (2013) [24]	6 weeks exercise training	22 cardiac rehabilitation patients	n.s.	n.s.	n.s.
Libardi et al. (2012) [25]	4 months exercise training (resistance,endurance, concurrent)	34 sedentary middle-age men	n.s.	n.s.	n.s.
Reed et al. (2010) [26]	4 months exercise training and caloric restriction (aerobic training)	Premenopausal women	n.s.	n.s.	↓
Andersson et al. (2010) [27]	14 days cross-country skiing tour endurance (12-30km/day)	20 men	↑ ↑	↑ ↑	n.s.

Beavers et al. (2010) [28]	12 months moderate intensity training	200 elderly	n.s.	---	---
Balducci et al. (2009) [29]	12 months high intensity (aerobic, aerobic/resistance) training	20 with type 2 diabetes	↓	↓	---
Castellano et al. (2008) [30]	8 week cycle-ergometry	11 with multiple sclerosis	↑ ↑	---	↓
Lambert et al. (2008) [31]	12 week training (aerobic + resistance training)	8 obese elderly	↓	---	↓
Kadoglou et al. (2007) [32]	6 months aerobic training	60 overweight with type 2 diabetes	n.s.	↓	---
Aronson et al. (2004) [33]	Physical fitness evaluation	1.640 with metabolic syndrome	---	↓	---
Goldhammer et al. (2005) [34]	12 week aerobic exercise	28 with coronary disease	---	↓	↓
Lakka et al. (2005) [12]	20 week exercise training 3x/week	162 sedentary healthy with high initial CRP-baseline levels 490 with low or moderate initial CRP baseline levels	--- ---	↓ n.s.	--- ---
Milani et al. (2004) [35]	3 months cardiac rehabilitation and exercise training with weight reduction	277 with coronary heart disease	---	↓	---
Okita et al. (2004) [11]	2 months aerobic training with weight reduction	199 healthy women	---	↓	---
Present study	9 months recreational training	33 with type 2 diabetes and insulin regimen	↑ ↑	n.s.	n.s.

Table 7. Author(s), year, type and duration of exercise training, and study population; increase (↑□), decrease (↓), no measurement (---) or no significant change (n.s.) in plasma levels of TNF-alpha, CRP, and IL-6.

sCRP and IL-6

CRP is a blood inflammation marker, which may play a role in many chronic diseases, including heart disease, stroke, and diabetes. Sorting through available data about the clinical relevance of TNF-α, IL-6 and slightly raised CRP levels produces incomplete and sometimes contradictory information.

Several studies have shown that physical activity and cardiorespiratory fitness are inversely correlated to CRP [33] and that regular exercise significantly reduces circulating levels of CRP [11, 34]. Moreover, it is uncertain whether exercise has a direct effect on CRP levels independent of weight loss, which has been shown to reduce CRP levels consistently [36]. Several studies suggest that low physical fitness is associated with high levels of C-reactive protein (CRP), a marker of future cardiovascular events (see also Table 7).

Aronson et al. [37] could show a concomitant decrease of CRP levels with increasing levels of physical fitness in middle-aged subjects with metabolic syndrome. Exercise may have effects on weight, cardiorespiratory fitness, insulin sensitivity, lipid profile and immune system. Thus designing a clinical trial that examines the role of lifestyle interventions such as exercise in reducing CRP may

be inconclusive due to interacting effects. Few studies have examined the effect of exercise on elevated levels of inflammatory biomarkers in diabetic subjects and reported contrasting results in terms of efficacy and dependence on weight loss.

As most studies physical activity/exercise studies have been cross-sectional [4, 5, 6, 7, 33, 38] or have combined exercise with diet interventions [2, 21, 26, 39, 40, 41], it is presently unclear whether exercise training decreases CRP independently of weight loss. Moreover, the type, dose and intensity of physical long-term tolerated activity needed to obtain a significant anti-inflammatory effect in diabetes patients are largely unknown.

IL-6 is a cytokine involved in a number of immunological processes, but it is also linked to exercise and possibly energy status. During exercise, muscle IL-6 levels and plasma IL-6 levels are increased and further augmented when intramuscular glycogen levels are low. Recent studies have demonstrated that IL-6 is also released from adipose tissue in response to an exercise bout. Furthermore, IL-6 has been demonstrated to have a lipolytic effect, thus possibly playing a role in mobilisation of energy as free fatty acids (FFA) in response to exercise [42]. It has been hypothesized that IL-6 is released from skeletal muscle during exercise to act in a "hormonlike" manner and increases lipolysis from adipose tissue to supply the muscle with substrate [43].

In this study no relevant changes in s-CRP or IL-6 were seen. The recreational training two times a week did not decrease apparent factors of systemic inflammation. Maybe the intervention frequency and exercise intensity were not high enough. But considering the mean s-CRP baseline level of 4.14 ± 3.4 $mgxl^{-1}$, it is a debatable point whether an increased inflammation status was even present. Insofar the inapparent exercise effect on s-CRP and IL-6 can not be assessed.

A close correlation between CRP levels and glycated haemoglobin (HbA_{1c}) has been reported, suggesting an association between glycemic control and systemic inflammation among patients with diabetes. The patients in our study were well controlled with a mean HbA_{1c} value of 6.4 ± 0.76 % (46.45 mmol/mol), so controlling blood glucose levels may have contributed to low CRP levels at baseline as well.

Effects on cardio-vascular risk parameters (lipid profile and blood glucose)

In this study the patients were moving towards a slight weight loss. In this regard the recreational training had limited effects on weight. But it should not be disregarded that the majority of the diabetic patients complained a constant weight gain before joining this program. Weight gain was also the most important trigger for the acceptance of the exercise program. Insofar stagnant weight or minor weight loss can be seen as a success. Further in some patients hypoglycemia occurred due to exercise and others are apprehensive of hypoglycemia. This in turn was a welcome justification for higher glucose intake before or after sports. Finally this kind of exercise training causes no higher weight loss without improved and reduced nutrition and sports adapted medical management. The aim of our study was to look at the effects of recreational exercise on inflammatory and lipid parameters without the diluting effects of controlling diet and losing weight, which are also seen to lower inflammatory markers. The nine months recreational exercise training had no effects on HbA_{1c}. This can be explained in the same way.

For most type 2 diabetic patients over 60 years of age, physical training is not a feasible form of therapy because of other interfering diseases which may complicate or severely hinder all physical training apart from very low intensity exercise programs. Type 2 diabetic subjects are predisposed to cardiovascular disease and are characterised by hyperlipidemia. This study shows that long-term low intensity training can markedly improve the blood lipid profile as measured by decreased levels of triglycerides, LDL, and total cholesterol.

In regard of the study subjects´ low-density lipoprotein (LDL), cholesterol and triglyceride levels the nine months recreational exercise training resulted in marked improvements and protective effects, which are equivalent to a moderate drug or sustainable dietary intervention. The current guideline for LDL levels in individuals without systemic disease is <4 $mmolxl^{-1}$. In individuals with diabetes the primary goal is an LDL <2.6 $mmolxl^{-1}$. Compared to this goal, the higher mean LDL baseline level of 3.24 $mmolxl^{-1}$ could be reduced by the recreational training to 2.88 $mmolxl^{-1}$ and thus within the range of recommendations for diabetic individuals. The current goal of triglyceride levels <1.7 $mmolxl^{-1}$ in individuals with diabetes is also nearly reached due to this long-term training (2.1 vs. 1.82$mmolxl^{-1}$ after 9 months). The HDL levels were higher than the current guideline of >1.15$mmolxl^{-1}$ at baseline (1.22 $mmolxl^{-1}$) and could be raised to 1.24$mmolxl^{-1}$ after the 9 months training period. The total cholesterol could be markedly reduced from 5.18 to 4.92 $mmolxl^{-1}$ after 9 months and thus reached the primary goal of <5 $mmolxl^{-1}$.

Although the subjects had a priori good medical lipid management, a further reduction of LDL, cholesterol and triglyceride levels within the range of current guidelines for diabetic people could be achieved by this long-term recreational training over 9 months.

Effects on cardio-circulatory system and endurance capacity

Cardiovascular disease represents the main cause of morbidity and mortality in patients with type 2 diabetes. The nine months low-intensity training was sufficient to obtain significant effects on cardio-circulatory parameters. The major effects were related to a significant improvement of the all day circulatory capacity by 103 %.This can be explained by a very low training intensity at the beginning because even low grade training exposure could be maintained only for few minutes by most patients. Training capacity after the 9 months recreational training was 56 ± 19.6 watt for 30 min. The endurance capacity of the diabetic patients was initially

limited by presence or high degree of complicating diseases, poor pre-training fitness and physical inactivity. The marked decrease in blood pressure (142.4 : 81.6 vs. 135.6 : 76.7 mmHg) near to the current guideline values of <130:80 mmHg due to recreational exercise training is equivalent to a moderate medical intervention and acts sustainable relieving on cardio-circulation. Further the heart stress resulting from the combined effects of blood pressure and heart rate was markedly reduced. The endurance capacity was improved by 103 % without an increased heart stress. This is best shown by the cardiac load (rate-pressure product divided by 1000). The rate-pressure product may be used as an index of myocardial oxygen consumption during exercise [44]. According to this parameter the myocardial oxygen demand during training had been reduced by about 50 %.

These quite impressive results may have their explanation in the extremely detrained status of the diabetic patients, when an even moderate training impulse creates a relevant stimulus of physiological reaction and has such marked and sustained cardio-circulatory effects.

5. Conclusion

This moderate exercise training program finally results in a 100 % higher cardio-pulmonary capacity after 9 months. The heart stress was reduced by 50 %. The significance of the increase in TNF-α levels by about 20 % remains unclear and requires further investigations

6. References

1. Bastard JP, Maachi M, Lagathu C et al. (2006) Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw 17: 4-12
2. Heilbronn LK, Campbell LV (2008) Adipose tissue macrophages, low grade inflammation and insulin resistance in human obesity. Curr Pharm Des 14: 1225-1230
3. Nishimura F, Soga Y, Iwamoto Y, Kudo C, Murayama Y (2005) Periodontal disease as part of the insulin resistance syndrome in diabetic patients. J Int Acad Periodontol 7: 16-20
4. Geffken DF, Cushman M, Burke GL, Polak JF, Sakkinen PA, Tracy RP (2001) Association between physical activity and markers of inflammation in a healthy elderly population. Am J Epidemiol 153: 242-250
5. Ford ES (2002) Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. Epidemiology 13: 561-568
6. LaMonte MJ, Durstine JL, Yanowitz FG et al. (2002) Cardiorespiratory fitness and C-reactive protein among a tri-ethnic sample of women. Circulation 106: 403-406
7. Church TS, Barlow CE, Earnest CP, Kampert JB, Priest EL, Blair SN (2002) Associations between cardiorespiratory fitness and C-reactive protein in men. Arterioscler Thromb Vasc Biol 22: 1869-1876
8. Festa A, D´Agostino JR, Williams K, Karter AJ, Mayer-Davis EJ, Tracy RP et al. (2001) The relation of body fat mass and distribution to markers of chronic inflammation. Int J Obes Relat Metab Disord 25: 1407-1415
9. Dos Santos MG, Pegoraro M, Sandrini F, Macuco EC (2008) Risk factors for the development of atherosclerosis in childhood and adolescence. Arq Bras Cardiol 90: 276-283
10. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB (1999) Elevated C-reactive protein levels in overweight and obese adults. JAMA 282: 2131-2135
11. Okita K, Nishijima H, Murakami T et al. (2004) Can exercise training with weight loss lower serum C-reactive protein levels? Arterioscler Thromb Vasc Biol 24: 1868-1873
12. Lakka TA, Lakka HM, Rankinen T et al. (2005) Effect of exercise training on plasma levels of C-reactive protein in healthy adults: the HERITAGE Family Study. Eur Heart J 26: 2018-2025
13. Rush EC, Plank LD, Yajnik CS (2007) Interleukin-6, tumor necrosis factor-α and insulin relationships to body composition, metabolism and resting energy expenditure in a migrant Asian Indian population. Clin Endocrinol 66: 684-690
14. Zavaroni I, Numeroso F, Dongiovanni P et al. (2003) What is the contribution of differences in three measures of tumor necrosis factor-α activity to insulin resistance in healthy volunteers? Metabolism 52: 1593-1596
15. Behre CJ, Fagerberg B, Hulten LM, Hulthe J (2005) The reciprocal association of adipocytokines with insulin resistance and C-reactive protein in clinically healthy men. Metabolism 54: 439-444

16. Zinman B, Hanley AJ, Harris SB, Kwan J, Fantus IG (1999) Circulating tumor necrosis factor-α concentrations in a native Canadian population with high rates of type 2 diabetes mellitus. J Clin Endocrinol Metab 84: 272-278

17. Pedersen BK, Bruunsgaard H (2003) Possible beneficial role of exercise in modulating low-grade inflammation in the elderly. Scand J Med Sci Sports 13: 56-62

18. Steensberg A, Fischer CP, Keller C, MØller K, Pedersen BK (2003) IL-6 enhances plasma IL-ra, IL-10, and cortisol in humans. Am J Physiol Endocrinol Metab 285: 433-437

19. Puglisi MJ, Fernandez ML (2008) Modulation of C-reactive protein, Tumor necrosis factor-α, and adiponectin by diet, exercise, and weight loss. J Nutr 138: 2293-2296

20. Carey AL, Bruce CR, Sacchetti M et al. (2004) Interleukin-6 and tumor necrosis factor-alpha are not increased in patients with type 2 diabetes: evidence that plasma interleukin-6 is related to fat mass and not insulin responsiveness. Diabetologia 47: 1029-1037

21. Loria-Kohen V, Fernández- Fernández C, Bermejo LM et al. (2013) Effect of different exercise modalities plus a hypocaloric diet on inflammation markers in overweight patients: a randomised trial. Clin Nutr 32: 511-518

22. Nikseresht M, Sadeghifard N, Agha-Alinejad H, Ebrahim K (2014) Inflammatory markers and adipocytokine responses to exercise training and detraining in men who are obese. J Strength Cond Res 28: 3399-3410

23. Donges CE, Duffield R, Guelfi KJ et al. (2013) Comparative effects of single-mode vs. duration-matched concurrent exercise training on body composition, low-grade inflammation, and glucose regulation in sedentary, overweight, middle-aged men. Appl Physiol Nutr Metab 38: 779-788

24. Kim HJ, Oh JK, Kim C et al. (2013) Effects of six-week cardiac rehabilitation and exercise on adiponectin in patients with acute coronary syndrome. Kardiol Pol 71: 924-930

25. Libardi CA, De Souza GV, Cavaglieri CR, Madruga VA, Chacon-Mikahil MP (2012) Effect of resistance, endurance, and concurrent training on TNF- α, IL-6, and CRP. Med Sci Sports Exerc 44: 50-56

26. Reed JL, De Souza MJ, Williams NI (2010) Effects of exercise combined with caloric restriction on inflammatory cytokines. Appl Physiol Nutr Metab 35: 573-582

27. Andersson J, Jansson JH, Hellsten G, Nilsson TK, Hallmans G, Boman K (2010) Effects of heavy endurance physical exercise on inflammatory markers in non-athletes. Atherosclerosis 209: 601-605

28. Beavers KM, Hsu FC, Isom S et al. (2010) Long-term physical activity and inflammatory biomarkers in older adults. Med Sci Sports Exerc 42: 2189-2196

29. Balducci S, Zanuso S, Nicolucci A et al. (2009) Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. Nutr Metab Cardiovasc Dis 20: 608-617

30. Castellano V, Patel Dim White LJ (2008) Cytokine responses to acute and chronic exercise in multiple sclerosis. J Appl Physiol 104: 1697-1702

31. Lambert CP, Wright NR, Finck BN, Villareal DT (2008) Exercise but not diet-induced weight loss decreases skeletal muscle inflammatory gene expression in frail obese elderly. J Appl Physiol 105: 473-478

32. Kadoglou NP, Iliadis F, Angelopoulou N et al. (2007) The anti-inflammatory effects of exercise training in patients with type 2 diabetes mellitus. Eur J Cardiovasc Prev Rehabil 14: 837-843

33. Aronson D, Sella R, Sheik-Ahmad M et al. (2004) The association between cardiorespiratory fitness and C-reactive protein in subjects with the metabolic syndrome. J Am Coll Cardiol 44: 2003-2007

34. Goldhammer E, Tanchilevitch A, Maor I, Beniamini Y, Rosenschein U, Sagiv M (2005) Exercise training modulates cytokines activity in coronary heart disease patients. Int J Cardiol 100: 93-99

35. Milani RV, Lavie CJ, Mehra MR (2005) Reduction in C-reactive protein through cardiac rehabilitation and exercise training. J Am Coll Cardiol 45: 1563-1569

36. Selvin E, Paynter NP, Erlinger TP (2007) The effect of weight loss on C-reactive protein: a systemic review. Arch Intern Med 167: 31-39

37. Aronson D, Sheikh-Ahmad M, Avizohar O et al. (2004) C-Reactive protein is inversely related to physical fitness in middle-aged subjects. Atherosclerosis 176: 173-179

38. Albert MA, Glynn RJ, Ridker PM (2004) Effect of physical activity on serum C-reactive protein. Am J Cardiol 93: 221-225

39. Esposito K, Pontillo A, Palo CD, et al. (2003) Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women a randomized trial. JAMA 289:1799-1804

40. You T, Berman DM, Ryan AS et al. (2004) Effects of hypocaloric diet and exercise training on inflammation and adipocyte lipolysis in obese postmenopausal women. J Clin Endocrinol Metab 89: 1739-1746

41. Nicklas BJ, Ambrosius W, Messier SP, et al. (2004) Diet-induced weight loss, exercise, and chronic inflammation in older, obese adults: a randomized controlled clinical trial. Am Clin Nutr 79: 544-551

42. Keller C, Keller P, Marshal S, Pedersen BK (2003) IL-6 gene expression in human adipose tissue in response to exercise-effect of carbohydrate ingestion. J Physiol 550: 927-931

43. Holmes AG, Watt MJ, Febbraio MA (2004) Suppressing lipolysis increases interleukin-6 at rest and during prolonged moderate-intensity exercise in humans. J Appl Physiol 97: 689-696

44. Gobel FL, Norstrom LA, Nelson RR, Jorgensen CR, Wang Y (1978) The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. Circulation 57: 549-556

Address for correspondence

Authors : Dr. med. dent. Antina Schulze - *Institute of Sports Medicine University of Leipz*

E-mail : a.schulze@uni-leipzig.de