

Connection between alterations of retinal vessels caused
by hypertension and life style modification (included
forced physical activity and diet) in adolescents

Thesis

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INTRODUCTION

Hypertension the risk factor of atherosclerosis, frequently a part of the metabolic syndrome which is a group of risk factors and important cause of the cardiovascular morbidity and mortality were found in adolescents, too. Sometimes, no symptoms are observed, sometimes organic changes as for example the pathologic alteration of retinal vessels show the effect of hypertension. Both primer and secunder hypertension were found in adolescent ages. Later is frequently the consequence of renal disease and improved after the end of the renal illness. Primer hypertension not detected in adolescent ages frequently causes cardiovascular risk in adult ages, why primary hypertension is mainly the subject of investigations dealing with the prevention of atherosclerosis in adolescent ages.

Primer hypertension is mostly essential, the punctual cause is known only in cases combined with overweight. Frequently found overweight and hypertension together. The exact gene defect has not known up till now, but familial occurrence is well known. Close connection were found between primary hypertension and metabolic illnesses as parts of the metabolic syndrome. Connections were found between plasma insulin level and blood pressure or pathologic serum lipid levels and hypertension.

Investigation of the retinal vessels shows both pathologic alterations caused by hypertension, and effect of different interventions. Well known the fundus hypertonicus in adults. The first grade retinopathy was described in children and adolescents with diabetes mellitus but not in children or adolescents with essential hypertension. The reversibility of the first grade retinopathy was described earlier, too.

Important purpose of the cardiovascular prevention is the life style modification included dietary changes and everyday physical exercise because of the lack of knowledge about the exact cause of the essential hypertension. The base of the dietary intervention is the low salt and low fat diet. As a consequence of these interventions alterations were observed in the metabolism and the blood pressure

decreased. Investigation of the fundus of the eye may help the observation of the intervention effects.

PURPOSES

- 1) Investigation of the fundus of the eye before and after everyday physical exercise applied by a fixed scheduled program.
- 2) Results of point 1) are observed together with body mass index (BMI), metabolic parameters and the applied diet.
- 3) Observation of early organ alterations caused by the metabolic syndrome according to the fundus of the eye of children and adolescents with overweight, hyperinsulinemia and insulin resistance.
- 4) According to the earlier described connection between physical activity and free oxygen radicals we search for common features of alterations of the fundus of the eye and one parameter of the lipid peroxidation the plasma thiobarbituric acid reactive system (TBARS).
- 5) Search for intervention which effect retinal vessels.
- 6) Search for parameters and results on the base of which the investigation of the fundus of the eye may necessary during preventive screenings.

METHODS AND PERSONS

Persons were investigated in 4 periods – altogether 822 children and adolescents (400 girls, 422 boys, age 5-18 yrs mean age: 15.2 yrs, BMI mean: 25.4 kg/m², 59% of BMI>95 centiles).

- 1) In order to check the usefulness of the equipment the fundus of the eye of 93 high school student was investigated in the **first period** by both an ophthalmoscope and the fundus camera connected with a personal computer. The 93 adolescents w/o any cardiovascular family risk had no hypertension.

Children and adolescents were investigated in the 2-4 periods sent to the outpatient service of 2nd Pediatric Department, Medical Faculty, Semmelweis University, or Heim Pál Pediatric Hospital because of their high cardiovascular family risk and/or hypertension or overweight. Their systolic blood pressure (SBP) was higher than 95 centiles. Exclusion criteria were secunder hypertension or other chronic illness and mental retardation disturbing the cooperation.

- 2) Adolescents with higher than 95 centiles office measured SBP were investigated in the **second period** (177 girls, 215 boys, total number. 392, age 10-18 yrs,) by 24 hours long ambulatory blood pressure monitoring (ABPM) and ophthalmologic investigation for the observation of the frequency of retinopathy in hypertension improved by ABPM and in the so called “white coat” hypertension.
- 3) Children and adolescents were investigated in the **third period** (61 girls, 53 boys, total: 114, age 5-17 yrs) for the observation of the effect of a **2 years** long life modification care (including diet and physical exercise together) on both the insulin resistance syndrome (IR) with hypertension in it and the retinopathy. Criteria of IR: hyperinsulinemia, insulin resistance, hypertension and two from the following further symptoms: serum total triglyceride (TT) is high, or serum high density lipoprotein cholesterol (HDL) is low, or BMI higher than 95 centiles. Persons were divided in 3

subgroups according to their plasma glucose (PG) level determined 120 and 180 minutes after the orally consumption of glucose (oral glucose tolerance test=OGTT)

3a) subgroup consisted of persons with $PG < 5,5$ mmol/L 180 minutes after the start of OGTT, no IR was observed in this subgroup.

3b) subgroup consisted of persons with $PG > 5,5$ mmol/L 180 minutes after the start of OGTT but $PG < 7,8$ mmol/L 120 minutes after the start of OGTT. Disturbance of the carbohydrate metabolism was observed in this subgroup, but no impaired glucose tolerance (IGT) was found.

3c) subgroup consisted of persons with $PG > 7,8$ mmol/L 120 minutes after the start of OGTT. This was the IGT subgroup.

Essential hypertension was observed rarely in children before their 10 yrs of age. We investigated 8 patients only from the 5-9 yrs age group and no retinopathy was found. The number of these children seems to be not enough for the statistical analysis why we speak about adolescents in both the title and in the discussion of the results of this thesis.

- 4) Adolescents were investigated in the **fourth period** (112 girls, 111 boys, total number: 223, age. 10-17 yrs, Tanner stage 2 or more) for the observation of the effect of **one year** long life modification (including diet with and w/o everyday usual physical exercise) on metabolic parameters, BMI, hypertension and retinopathy searching for answers of two questions: 1) how long we have to continue the life modification process for the improvement of the retinopathy? 2) is the diet enough alone, what is the role the everyday physical exercise in the intervention process? Adolescents having similar diet were divided into 2 subgroups according to their physical activity.

4a) subgroup consisted of adolescents (53 girls, 55 boys, total number: 108) decided an everyday physical exercise

according to a fixed scheduled program accommodated to the personal possibilities

4b) adolescents belonging to this group on similar diet as subgroup 4a w/o usual physical exercise (some of them took part in official high school curriculum, some of them not, 59 girls, 56 boys).

Clinical investigations included the measurement of height, weight and blood pressure determined office and by ABPM were performed in the 3rd period at the start and end and 2, 8, 14, 20 month after the start and in the fourth period at the start and the end.

Laboratory measurements: apart from blood count, ESR and the investigation of the kidney function fasting plasma insulin (PI) (by IMX automatic method) serum total cholesterol (TC), HDLC, TT, fasting and in the 3rd period after OGTT measured PG (by Hitachi automatic method), in the 4th period serum apo-A-I, apo- B (by turbidimetric method) and TBARS (by fluorimetric method) were determined. BMI, serum low density lipoprotein cholesterol (LDLC) (by Friedewald method because the serum TT level was lower than 4 mmol/L), homeostasis model assessment (HOMA), and in the 3rd period oral glucose insulin sensitivity (OGIS) were calculated.

The **fundus of the eye** was investigated by Topcon Imagenet PAL for Windows Compact Digital Imaging System. The equipment consisted of a 45° TRC-NW 5D nonmydriatic camera, and a Sony DXC 950P 800x600 PAL digital camera, Windows based Pentium PC hardware and Imagenet Lite software. Results of blood pressure measurements and ophthalmologic investigations were compared at the end of periods.

Diameter of arterial and venous pairs performed in 4 – 4 place of the same fundus in a distance from the optic disc which equal of the diameter of optic disc. The distance was measured manually. Arterial-venous ratio was calculated, and narrow arteries were stated if the ratio was 0.5 or < 0.5. Arteries were observed for the determination of Guist symptom, too. We spoke about Guist symptom if 3 or more alterations were found in a distance from optic disc which equal 3 diameter of the optic disc. Gunn symptoms when the arteries are above veins were found very rarely.

Methods of the **life modification** were the following: **diet** was offered and controlled in which the total absorbed energy daily from fat, carbohydrate, protein and saturated fatty acid were 25-35%, 45-65%, 10-30% and 10%, respectively. Total cholesterol consumption was 300 mg/day. The vegetable and fiber rich food consisted no dressing. Salt consumption was 6 mmol/kg daily or lower because spices were used for the good taste of the food instead of salt. The common family food consumption consisted more breakfast than dinner. Low fat dairy products, water and home made fruit juice were used as drinks.

The **everyday physical exercise** was performed by a controlled fixed scheduled program accommodated to every person depending on BMI and family possibilities during 60 minutes or more daily consisted of aerobic features: playing with balls, running, dancing, climbing to the hills, walking and riding on bicycles. One person can change the form of the physical activity during the care period. The possibility of the dizziness of adolescents with hypertension was calculated when the physical exercise plan was made.

The earlier observed **active and passive smoking** was not more found in the participants.

RESULTS

Investigations in the **first period** showed the similarity of results obtained by funduscopy or by fundus camera connected with a PC, but later gave more objective pictures and a possibility of both the storage and a possibility of the compare of pictures made different times about the same fundus.

Early signs of retinopathy.

According to observations during the **second period** 164 adolescents (69 girls and 95 boys) had SBP higher than 95 centiles measured by both office and ABPM method from 392 adolescents whose high SBP was measured in the school (2a subgroup). 66 of them showed retinopathy (wide veins, narrow arteries or arteries with other pathologic features). Only 5 adolescents showed retinopathy from 228 adolescents (108 girls and 120 boys) whose high SBP was not improved by ABPM (2b subgroup). The difference of frequency found between two subgroups was significant (Result of Fisher test: $p < 0.0001$, possibility ratio 30.04 (11.73-76.88), relative risk 18.35 (7.559-44.55, confidency interval: 95%). Fundus investigation may show the difference between two subgroups.

No statistically significant difference was found between girls and boys in any periods.

Dipper ABPM results were found, SBP was 10% lower in night than that in daytime. High diastolic blood pressure was not found.

Connections between IR, SBP and retinopathy during the 2 yrs long care.

Connections between IR and retinopathy and the effect of two years long life modification (diet and physical exercise together) were investigated in the **third period** when 114 children and adolescents were investigated. 1 adolescent had type 2 diabetes mellitus, another had impaired fasting glucose both adolescents were not participant of further calculations. 93 investigated persons had a BMI more than 95 centiles. The two years long care was refused by 15 families. The two years long care started in 97 patients divided into 3 subgroups.

IR was not found in 3a subgroup (27 adolescents), but it was found in 40 adolescents (79%) from 51 patients belonging to the 3b subgroups and 15 adolescents (78%) from 19 patients belonging to 3c subgroup. No significant difference was found between 3b-3c subgroups. 12 adolescents showed IR (80%) from 15 patients who decided no participation in the 2 years long life modification program.

After the 2 years long care the following alterations were found independently from the BMI at the start: mean of BMI changed from 29.2 kg/m² to 25.9 (p<0.001), mean serum TT diminished from 1,3 mmol/L to 1,0 (p=0.008), mean serum HDLC increased from 1.2 mmol/L to 1,5 (p<0.001), mean fasting PI decreased from 16.2 mU/L to 13.1 (p=0.033), mean HOMA changed from 4.1 to 3.4 (p=0.006), mean OGIS increased from 435 to 506 (p<0.001), other significant changes were not found in mean PG, serum TC or LDLC levels which were normal at the start and the end. No significant changes were found after two years in group of adolescents w/o participation in the care.

Retinopathy was found in the fundus of the eye of 18 adolescents from 47 patients with high SBP participated in the 2 years long care (15 belonging to 3b and 3 belonging to the 3c subgroups). No retinopathy in adolescents with normal SBP or w/o IR was found. Adolescents refusing the participation in the two years long care had high SBP in 7 (from 15) cases. Retinopathy was found in 3 cases from 7 patients with high SBP. After the 2 years long care the mean of SBP decreased from 131 Hgmm to 120 (p<0.001), the earlier normal diastolic blood pressure did not change. No retinopathy was found after the care but the earlier retinopathy was found in 3 adolescents refused the participation in the care.

Effects of one year long everyday physical activity.

Hypertensive adolescents (112 girls, 111 boys, altogether 223 persons, age: 10-17 years, Tanner stage 2 or more) having the same diet were observed during one year in the **fourth period**. They were divided into 2 subgroups according to their physical activity. 4a subgroup consisted of 108 adolescents (53 girls, 55 boys) on low fat, low salt diet who every day during almost 60 minutes took part in an

intensive physical activity according to a fixed scheduled program accommodated to the personal and familial possibilities, 4b subgroup consisted of 115 adolescents (59 girls, 56 boys) on similar diet but they did not take part in similar physical exercise program, some of them took part in the official physical exercise curriculum 2 times a week in the high school, some of them did not take part in any physical exercise program.

Similar frequency of I. grade retinopathy was found in both subgroups at the start of the period. The frequency did not differ due to the gender of adolescents. In subgroup 4a 19 girls and 18 boys altogether 37 cases, in subgroup 4b 15 girls and 17 boys, altogether 32 cases had retinopathy. After one year of everyday physical activity in 4a subgroup 5 girls and 3 boys, altogether 8 cases had the same retinopathy, w/o everyday physical activity in 4b subgroup 13 girls and 14 boys altogether 27 cases showed the same alteration of the fundus of the eye than one year earlier. The difference between the 2 subgroups was significant ($p < 0.001$).

Similar decrease of mean serum apo-B, TC, TT, LDLC and PI, HOMA, SBP and BMI, and increase of mean serum apo-A-I and HDLC levels was observed in both subgroups as it was found in the third period after a 2 year long care, too.

Mean plasma TBARS levels decreased in both subgroups, but the decrease was much higher in subgroup 4a than that in subgroup 4b so that significant difference was found between mean TBARS levels found in 4a and 4b subgroups which was not observed at the start of the period. At the end of period mean plasma TBARS level was 1.9 nmol/mL and 2.6 nmol/mL in group 4a and 4b, respectively ($p < 0.02$).

CONSEQUENCES

Retinopathy observed in adolescents with high SBP was improved after a two years long life modification care (included diet and physical exercise). If the care was one year long the improvement was due to the everyday intensive physical exercise which show the important role of the everyday physical activity in the treatment of retinopathy caused by hypertension.

Retinopathy was observed only in adolescents with IR where the hypertension was one symptom of IR. There were several adolescents with hypertension w/o retinopathy which show the important role of the carbohydrate and fat metabolic changes, too in the development of retinopathy.

Changes of cardiovascular risk factors (decrease of SBP, BMI, fasting serum TT, apo-B, HOMA and PI, increase of HDLC, OGIS and apo A-I) showing the usefulness of the applied care (diet and physical exercise together). Normal values of fasting PG, diastolic blood pressure, serum TC, LDLC has not changed during and after care.

Plasma TBARS of adolescents after one year long everyday physical activity decreased in significantly higher extent than that of adolescents on the same diet w/o everyday physical activity. This observation was similar than that observed with connection of retinopathy. The improvement of retinopathy may be connected with the decrease of free radicals as an effect of physical exercise. This possible connection would be important in overweight adolescents with more oxygen free radicals.

Retinopathy observed in hypertensive adolescents is promoted by IR and may be the too lot of free radicals. Alterations observed in vessels are reversible effected by life modification (diet and physical exercise) from which the everyday physical exercise seems to be the most effective tool.

About one third of hypertensive adolescents had reversible retinopathy which improved with non pharmacologic treatment.

Practical consequences

Ophthalmologic investigation is necessary of every adolescent with high SBP especially if the hypertension is a part of IR. More objective investigation is necessary if retinopathy suspected as a result of funduscopy.

Ophthalmologist observed retinopathy of the patient have to offer a pediatric metabolic investigation in order to prevent the later cardiovascular problems especially in cases with high atherosclerotic family risk.

NEW RESULTS

Fundus camera connected with a personal computer by a special software show similar pictures about the fundus of the eye as funduscopy with a possibility of a more objective picture and the storage and comparison of different pictures.

The retinopathy is significantly more frequent in adolescents with essential hypertension than that in adolescents with “white coat” hypertension.

Retinopathy is usually observed in hypertensive adolescents with IR.

Parallel changes were observed after a one year long period between the improvement of retinopathy and the decrease of plasma TBARS which may show the connection between retinopathy and some oxidative processes.

First grade retinopathy in adolescents with essential hypertension treated by non pharmacologic treatment is a reversible process.

From the part of life modification treatment the everyday physical exercise is the most effective method for the improvement of retinopathy.

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