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**URINALYSIS FINDINGS, OBESITY AND
HYPERTENSION IN ITALIAN ADOLESCENTS
FROM WORLD KIDNEY DAY**

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MAIN OBJECTIVES OF WORLD KIDNEY DAY

World Kidney Day (WKD) started in 2006 by a memorandum of understanding between the International Federation of Kidney Foundations (IFKF) and the International Society of Nephrology (ISN) based on a proposal to “raise awareness of the importance of our kidneys to our overall health and to reduce the frequency and impact of kidney disease and its associated health problems world-wide”(1-2).

WKD was conceived to inform the general population of the fact that chronic kidney disease is a global, public health threat that frequently occurs with no symptoms, and which can be treated with early detection using simple and inexpensive methods(1). The need for a WKD devoted to kidney diseases arises also from the knowledge that most people are unaware of their blood pressure and the potential presence of abnormalities in their urine. Indeed, some surveys have shown that less than 5% of the general population know where the kidneys are located and which is their function(1).

In recent years WKD has grown considerably up to being now the most celebrated event associated with kidney disease in the world(3). Many countries participate by organizing health screening events, public lectures, press conferences, political activities and other efforts.

Chronic kidney disease (CKD) affects about 10% of the adult general population, and recently, it has been estimated that at birth the overall lifetime risk of CKD stage 3a is about 60%(4).

This high prevalence rate, together with the elevated cost of treatment and the fact that preventive measures are not yet fully in place, makes CKD a public health problem(5).

Moreover, the link between CKD and cardiovascular disease (CVD) is well established, and the number of people with both kidney disease and CVD continues to climb at an alarming rate. Indeed, CKD accelerates the progression of heart disease and increases the likelihood of major cardiovascular events and related death(6). Therefore, it is of vital importance to prevent and treat kidney diseases also to decrease cardiovascular morbidity and mortality.

By considering the complex interrelationship between CKD and preventable risk factors, such as hypertension, obesity, dyslipidemia and smoking, a screening program must occur at primary care level, also because there is consistent evidence that progression of CKD can be reduced by changing lifestyle, controlling blood pressure (BP) and using kidney protective drugs(7,8).

These are the main reasons for the IFKF and FIR actively promoting WKD as a valuable prevention program.

Different topics that have been treated from years 2006 to 2014 were reported in Fig. 1.

The WKD promoters suggest eight golden rules to reduce the risk of developing kidney disease(9):

- Keep fit and active
- Control blood sugar level
- Monitor blood pressure
- Eat healthy and check weight regular
- Reduce salt intake
- Maintain a healthy fluid intake
- Do not smoke
- Do not take over-the-counter pills on a regular basis as non-steroidal anti-inflammatory drugs
- Check kidney function in healthy persons with ‘high risk’ factors as diabetes, hypertension, obesity, history of kidney disease.

In Italy the WKD was planned and conducted by the Fondazione Italiana del Rene (FIR; National Kidney Foundation of Italy), in collaboration with the Italian Society of Nephrology (SIN) and the Red Cross of Italy.

Italian WKD focused on two projects called ”Square project” and “School project”. The “Square project” was intended for general population and the “School project” for students attending the fourth and fifth year of Italian high school.

The “Square project” was organized with mobile clinics or gazebos with an examination room and restrooms for urine collection. Mobile clinics or gazebos were parked in a central square of the participant cities.

The “School project” was carried out in several Italian cities and trained personnel (nephrologists and nurses) assessed systolic and diastolic blood pressure.

This is a unique initiative in the context of those carried out around the world by countries that have observed WKD. The relevance of this screening relies on the fact that this population is seldom evaluated by either pediatricians or general practitioners in the absence of overt disease. Paradoxically, adolescents, because of having a longer life expectancy than adults, are more exposed to risk factors(10). Therefore, early detection of their urinary abnormalities and/or abnormal blood pressure levels allows action to be taken to reduce the risk of irreversible disease years later.

To perform this nationwide survey in Italian students, permission was asked of the headmasters of high schools for using school facilities, and informed consent was obtained for parents for minor age students.

RELEVANCE OF URINE ANALYSIS IN THE ASSESSMENT OF KIDNEY DISEASES

Urinary diagnostic assessment is an important screening method to detect kidney diseases, along with measurement of blood pressure and physical examination.

DIPSTICK TEST

Dipstick urinalysis is most commonly performed to diagnose urinary tract infection or to detect renal disease. Abnormal findings in urinalysis can be seen in 1 - 14% of healthy adolescents(11-14).

False-positive and false-negative results are frequent in dipstick urinalysis because there are many substances interfering with test reagents. Nonetheless, the sensitivity and specificity of this test in detecting microscopic hematuria and significant proteinuria is respectively 91% - 61% and 96% - 87%(15- 24).

The basic requirements for the interpretation of urinalysis findings are the correct acquisition of the sample and the correct performance of tests. Dipstick tests can be used to detect leukocyturia, proteinuria, glycosuria and hematuria.

DIPSTICK TEST AND PROTEINURIA

Proteinuria—excessive elimination of protein in the urine—can indicate tubular or glomerular dysfunction. Dipstick tests provide only semiquantitative findings because they do not take into account the renal filtration rate and mainly disclose the presence of albumin, in semiquantitative fashion.

Albuminuria is the well-established indicator of structural changes induced by kidney injury. It is worth mentioning that albuminuria is widely used not only in the diagnosis and classification of chronic kidney disease (CKD) but also as a symptom of endothelial injury in hypertension, diabetes and cardiovascular disease (CVD)

In healthy persons, the glomerular capillary wall is permeable only to substances with a molecular weight of less than 20,000 Daltons. After being filtered, low-molecular-weight proteins are reabsorbed and metabolized by the proximal tubule cells. Normal urinary proteins include albumin, serum globulins, and proteins secreted by the nephron. Proteinuria is defined as urinary protein excretion of more than 150 mg per day (10 to 20 mg per dL) and is the hallmark of renal disease. Microalbuminuria is defined as the excretion of 30 to 150 mg of protein per day and is a marker of early renal disease, particularly in diabetic patients.

The dipstick tests reagent is mostly sensitive to albumin but may not detect low concentrations of γ -globulins and Bence-Jones proteins. Dipstick tests for trace amounts of protein yield positive results at concentrations of 5 to 10 mg per dL, lower than the threshold for clinically significant proteinuria(25). A result of 1+ corresponds to approximately 30 mg of protein per dL and is considered positive; 2+ corresponds to 100 mg per dL, 3+ to 300 mg per dL, and 4+ to 1,000 mg per dL(26-27). Dipstick urinalysis reliably can predict albuminuria with sensitivity and specificity of greater than 99 percent(28). Asymptomatic proteinuria is associated with significant renal disease in less than 1.5 percent of patients(28,29).

Proteinuria can be classified as transient or persistent(30). In transient proteinuria, a temporary change in glomerular hemodynamics causes the protein excess; these conditions follow a benign, self-limited course(31,32).

Orthostatic (postural) proteinuria is a benign condition that can result from prolonged standing; it is confirmed by obtaining a negative urinalysis result after eight hours of recumbency.

Persistent proteinuria is divided into three general categories: glomerular, tubular, and overflow. In glomerular proteinuria, the most common type, albumin is the primary urinary protein. Tubular proteinuria results when

malfunctioning tubule cells no longer metabolize or reabsorb normally filtered protein. In this condition, low-molecular-weight proteins predominate over albumin and rarely exceed 2 g per day. In overflow proteinuria, low-molecular-weight proteins overwhelm the ability of the tubules to reabsorb filtered proteins.

Further evaluation of persistent proteinuria usually includes determination of 24-hour urinary protein excretion or spot urinary protein-creatinine ratio, microscopic examination of the urinary sediment, urinary protein electrophoresis, and assessment of renal function(27).

DIPSTICK TEST AND HEMATURIA

According to the American Urological Association, the presence of three or more red blood cells (RBCs) per high-powered field (HPF) in two of three urine samples is the generally accepted definition of hematuria(33-35). The dipstick test for blood detects the peroxidase activity of erythrocytes. However, myoglobin and hemoglobin also will catalyze this reaction, so a positive test result may indicate hematuria, myoglobinuria, or hemoglobinuria. Visualization of intact erythrocytes on microscopic examination of the urinary sediment can distinguish hematuria from other conditions. Microscopic examination also may detect RBC casts or dysmorphic RBCs. Hematuria is divided into glomerular, renal (i.e., non-glomerular), and urologic etiologies(30).

Glomerular Hematuria. Glomerular hematuria typically is associated with significant proteinuria, erythrocyte casts, and dysmorphic RBCs. However, 20 percent of patients with biopsy-proven glomerulonephritis present with hematuria alone(36). IgA nephropathy (i.e., Berger's disease) is the most common cause of glomerular hematuria.

Renal (Nonglomerular) Hematuria. Non-glomerular hematuria is secondary to tubule-interstitial, renovascular, or metabolic disorders. Like glomerular hematuria, it often is associated with significant proteinuria; however, there are no associated dysmorphic RBCs or erythrocyte casts. Further evaluation of patients with glomerular and non-glomerular hematuria should include determination of renal function and 24-hour urinary protein or spot urinary protein-creatinine ratio.

Urologic Hematuria. Urologic causes of hematuria include tumors, calculi, and infections. Urologic hematuria is distinguished from other etiologies by the absence of proteinuria, dysmorphic RBCs, and erythrocyte casts. Even significant hematuria will not elevate the protein concentration to the 2+ to 3+ range on the dipstick test(37). Up to 20 percent of patients with gross hematuria have urinary tract malignancy; a full work-up with cystoscopy and upper-tract imaging is indicated in patients with this condition(38). In patients with asymptomatic microscopic hematuria (without proteinuria or pyuria), 5 to 22% have serious urologic disease, and 0.5 to 5% have a genitourinary malignancy(39-43). Exercise-induced hematuria is a relatively common, benign condition that often is associated with long- distance running. Results of repeat urinalysis after 48 to 72 hours should be negative in patients with this condition(44).

DIPSTICK TEST AND LEUKOCYTURIA

Leukocyturia makes a urinary tract infection likely; as an isolated finding, it is highly sensitive (83%), but not very specific(45). The authors recommend microscopic analysis of a freshly obtained, native urine sample, because the leukocyte esterase reaction of urinary dipsticks is not a fully adequate substitute for microscopy, although there is some debate on this point in the literature(45-47). The leukocyte esterase test can be made positive by lysed leukocytes or sub-preputial material even when microscopy does not reveal any leukocytes; it can also be negative despite positive microscopic findings if the urine is highly concentrated or contains “collapsed” leukocytes(48).

Whatever is being tested, the instructions for use of the dipstick should be followed conscientiously. The leukocyte count per unit volume is affected by the variable amount of urine in each voiding. This can alter the findings not only of dipstick tests, but also of counting chambers and other cell-counting methods. A leukocyte count of 5–10/ μL is considered abnormal in boys over age 3; in girls, counts in the range of 20–50/ μL are suspect for a urinary tract infection, and counts above 50/ μL are considered clearly abnormal.

The microscopic demonstration of leukocyte cylinders in the urine sediment, together with marked bacteriuria, is pathognomonic for pyelonephritis.

DIPSTICK TEST AND GLYCOSURIA

Glucose normally is filtered by the glomerulus, but it is almost completely reabsorbed in the proximal tubule. Glycosuria occurs when the filtered load of glucose exceeds the ability of the tubule to reabsorb it (i.e., 180 to 200 mg per dL). Etiologies include diabetes mellitus, Cushing's syndrome, liver and pancreatic disease, and Fanconi's syndrome(49).

CLINICAL RELEVANCE OF OVERWEIGHT/OBESITY FOR INCEPTION AND PROGRESSION OF KIDNEY DISEASE

The incidence of high body weight, high body mass index (BMI) and obesity is increasing dramatically worldwide. Meanwhile, obesity represents an enormous public health problem not only in the Western world but also in many developing countries.

The World Health Organization and the National Heart, Lung, and Blood Institute define overweight as an "excess of body weight" and obesity as "an excess of fat."(50).

However, a more objective measure now provided by the World Health Organization defines overweight as a BMI of 25 kg/m² or greater and obesity as a BMI of 30 kg/m² or greater, with the following subcategories: class 1 (BMI, 30.0 - 34.9 kg/m²), class 2 (BMI, 35.0 - 39.9 kg/m²) and class 3 (BMI, > 40 kg/m²). Although objective measures to identify overweight and obesity are helpful, the implementation of BMI in clinical practice has created a unique set of problems. BMI tends to overestimate obesity in adults with a high degree of muscle mass. In addition, BMI does not address regional adiposity. As a result, use of BMI to define overweight and obesity may possess weak specificity and/or sensitivity in certain groups such as elderly patients, individuals with wasting conditions, athletes, and others(51).

Overweight and obesity are well-established risk factors for renal function loss. Several studies noted an association between obesity and progressive renal damage in subjects with renal disease(52), in renal transplant recipients(53-55) and even in the general population(56-60).

Subjects with obesity have a 5-fold increased risk for end-stage renal disease (ESRD) when compared with lean subjects(58). Moreover, a body mass index (BMI) over 25 kg/m² still carries a 2 to 3-fold elevated long-term risk of ESRD(58-59). Of note, a central body fat distribution is also associated with a detrimental long-term renal prognosis(61-62).

Several factors contribute to the adverse renal effect of weight excess. Overweight subjects have an increased risk of developing hypertension, dyslipidaemia, insulin resistance/ diabetes mellitus and cardiovascular complications, all of which promote CKD. However, even in the absence of these risks, obesity itself is associated with the development of CKD and accelerates its progression(59-60).

The abnormalities of renal structure in obese individuals include increased kidney weight, glomerulomegaly, disorder of podocytes, mesangial expansion, and, more recently, also abnormalities of the renal interstitium (ie, tubular atrophy and interstitial fibrosis), and accompanying vascular alterations. This is accompanied by an unfavorable renal haemodynamic profile such as renal hyperperfusion, increased filtration fraction, albuminuria, or proteinuria (61).

The renal haemodynamic profile in overweight and obesity, and in subjects with a central body fat distribution, can affect sodium and volume homeostasis, as well as long-term susceptibility to renal damage. Sodium homeostasis is closely interlinked with renal haemodynamics. High filtration fraction (FF), indicating a relatively high efferent vascular tone, is associated with blunted sodium excretion by reducing peritubular hydrostatic pressure and hence facilitating tubular sodium reabsorption. Thus, higher FF predisposes to ECV expansion, in particular during high sodium intake, and consequently to salt-sensitive hypertension. This is in line with older data on renal haemodynamics in salt-sensitive hypertension(62-63), and with the clinical association between weight excess and salt-sensitive hypertension, that is reversible by weight loss(64).

Interestingly, in young normotensive subjects, overweight is associated with a rise in FF in response to high salt intake, whereas in lean subjects GFR increases without a rise in FF. In overweight subjects, moreover, high salt intake is associated with a larger increase in the ECV than in lean subjects, supporting the impact of subtle changes in renal haemodynamics on volume homeostasis(65-66). The long-term consequences of this unfavorable renal haemodynamic profile, elicited by the combination of overweight and excess sodium intake, have not been documented, but it may well contribute to the development of salt-sensitive hypertension and renal damage later in life. Whereas the adverse effect of a high FF on renal damage has been well

documented in the rat remnant kidney model, human data on the association between an unfavorable renal haemodynamic pattern and long-term renal outcome are particularly sparse. There is only the report by Bosma et al., showing that high BMI was associated with both increased FF and worse death-censored graft loss in renal transplant recipients, and where higher FF was a predictor of worse graft outcome, independent of blood pressure and proteinuria(67). This provides support for the assumption that higher FF predisposes the kidney to progressive damage, but also suggests that the association is probably not straightforward, as higher FF was also associated with patient mortality.

Increased activity of the RAAS has been implicated in the renal haemodynamic profile in overweight and obesity(68). The reversibility by RAAS blockade is in line with this assumption(69). Interestingly, a higher BMI is also associated with a better long-term renal outcome of RAAS blockade, suggesting that inappropriately elevated RAAS activity is particularly involved in renal damage in overweight and obese subjects(70). The interaction between BMI, renal haemodynamics and sodium status suggests that overweight hampers the suppression of RAAS activity by high sodium intake and/ or volume expansion. Whereas this could not be substantiated for circulating components of the RAAS, tissue RAAS activity has been shown to be increased in obesity, and not suppressed by high sodium intake. Taken together, these data indicate that RAAS blockade would be a

rational pharmacotherapy for overweight or obese subjects with hypertension and or renal damage preferably combined with dietary sodium restriction. It would be logical to assume corresponding mechanisms for subjects with a central body fat distribution, but so far, no data are available. Yet, additional intrarenal factors may be involved, in particular increased glomerular and tubular dimensions(71).

In human beings, urine protein excretion decreases with weight loss regardless of blood pressure. It is possible that calorie restriction (which leads to weight loss) directly impacts proteinuria. One study randomized 30 overweight and obese adults with proteinuria and proteinuric kidney diseases (both diabetic and nondiabetic) to either a usual diet or calorie restriction of 500 kcal/d for 5 months(72).

Individuals randomized to calorie restriction lost approximately 4% of their baseline weight over a 5 month period, yet proteinuria decreased by more than 30%. Average urine protein excretion decreased from 2.8 g/d at baseline to 1.9 g/d among the calorie restricted group, whereas urine protein excretion tended to increase in the group without calorie restriction(72). As stated previously, significant renal hemodynamic changes appear to be limited to individuals who undergo bariatric surgery(73). It should be noted that for the first 6 to 12 months after bariatric surgery, calorie intake is reduced markedly owing to the marked decrease in stomach size. Thus, individuals who undergo bariatric surgery experience calorie restriction; GFR, ERPF, and urine protein excretion

all decrease after bariatric surgery despite the fact that individuals continue to be obese (albeit with a lower BMI)(74). It remains unknown whether these changes occur as a function of weight loss or calorie restriction or both.

The association between calorie restriction and kidney disease measures may be mediated by a member of the silent information regulator 2 protein family of enzymes found in all terrestrial life called Sirt1(75). The expression of Sirt1, a nicotinamide adenine dinucleotide-dependent deacetylase, is upregulated in the setting of calorie restriction." Sirt1 is expressed abundantly in the renal inner medulla and in medullary interstitial cells and likely protects medullary interstitial cells from oxidative stress(76). Mice lacking Sirt1 expression show more fibrosis and cellular apoptosis after unilateral ureteral obstruction compared with wild type mice that do not lack Sirt1 expression(76).

Sirt1 also may mediate the association between adiponectin and urine albumin excretion. As abdominal adiposity increases, adiponectin levels decrease,(77) while urine albumin excretion generally increases(78-81). Adiponectin receptors reside on podocytes and likely play a role in podocyte morphology and/or function because mice lacking adiponectin expression show effacement of podocyte foot processes and proteinuria(82). Adiponectin knockout mice also show stronger expression of vascular cell adhesion molecule-1, tumor necrosis factor alfa, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase compared with the wildtype mice with normal adiponectin

expression(83). Treatment of adiponectin knockout mice with adiponectin reduces albuminuria, podocyte effacement, inflammatory markers, and NADPH oxidase to levels commensurate with wild type mice(82,84). Sirt1 modulates expression of the cell cycle protein Foxo1 by deacetylating 3 lysine residues within the Foxo1 DNA binding domain. This activated Foxo1 then forms a transcriptional complex with CCAAT/enhancer binding protein alpha at the adiponectin promoter site and upregulates adiponectin gene expression(85). Sirt1 also activates endothelial nitric oxide synthase and increases bioavailable endothelial nitric oxide to reduce oxidative stress(86). Thus, a circuitous link exists whereby high calorie intake leads to decreases in Sirt1 expression, which then leads to down-regulation of adiponectin expression and decreased bioavailable endothelial nitric oxide. These factors then may impact podocyte function and/or morphology.

AIM OF SCHOOL PROJECT

The main goal of the present study was to assess the presence of urinalysis abnormalities and their associations with hypertension and obesity in a population of adolescents participating in the Italian Kidney Day during the period 2010–2011

METHODS

The study population consisted of 17 to 25-year-old students attending Italian high schools who participated in the Italian Kidney Day of years 2010 and 2011.

All students were invited to participate in the study. Written consent was requested to parents for minor-age students.

Data on age, gender, sport activity and general information was assessed using questionnaires. Students answered to a questionnaire that addressed to awareness of kidney function, kidney disease, hypertension, dialysis, kidney transplantation, diabetes and the meaning of the word proteinuria. Adolescents were also asked about the relevance they gave to measuring blood pressure or reducing body weight for their health.

A complete urine test was performed with a dipstick on specimens. Samples of urine were analyzed using urine dipstick for hematuria, proteinuria, leukocyturia and glycosuria.

Positive reactions were based on color change corresponding to color chart provided by the test strip's manufacturer. Subjects were considered proteinuric when urine dipstick was positive for proteinuria ≥ 30 mg/dL.

In the presence of an abnormal urinary dipstick and/or blood pressure result, participants were invited to contact either the nephrologists involved in the survey or their general practitioner for confirmation of data and further evaluation.

Weight and height was measured. We calculated the body mass index (BMI) = weight (kg) / height² (m²). According to BMI, normal weight was from 18.5 to 24.9 kg/m², overweight from 25 to 29.99 kg/m², class-I obesity from 30 to 34.99 kg/m², class-II obesity from 35-39.99 kg/m², class-III obesity > 40 kg/m².

Waist circumference (WC) was measured with an anthropometric fiberglass tape at the midpoint between the last rib and the iliac crest. Normal WC was considered <88 cm in female and <102cm in male.

The waist-to-height ratio (WHtR) was determined by dividing WC (cm) by height (cm) and the conicity index (C index) was determined by measuring weight, height and waist circumference using the following mathematical equation(87):

$$C \text{ Index} = \frac{\text{WaistCircumference(m)}}{0.109 \sqrt{\frac{\text{BodyWeight(kg)}}{\text{Height(m)}}}}$$

Blood pressure was checked by auscultation, which used a sphygmomanometer with appropriate cuff for the arm circumference, after the student remained five minutes at rest and sitting. The measurement was performed on the right arm at heart level in a seated position.

Systolic blood pressure (SBP) was determined at the onset of Korotkoff sounds (phase I), and diastolic blood pressure (DBP), at the disappearance of Korotkoff sounds (phase V).

Hypertensive subjects were considered those with systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg or they were taking antihypertensive medication.

Isolated systolic hypertension (ISH) was defined as SBP ≥ 140 mmHg and DBP ≤ 90 mmHg. Pre-hypertension (HTN) as SBP of 120 mmHg but lower than 140 mmHg or DBP of 80 mmHg but lower than 90 mmHg. Stage-1 HTN as SBP of 140 mmHg but lower than 160 mmHg or DBP of 90 mmHg but lower than 100 mmHg, and Stage-2 HTN as SBP ≥ 160 mmHg or DBP ≥ 100 mmHg.

STATISTICAL ANALYSIS

Descriptive statistics included frequencies and percentages or means with standard deviation errors (SD) for demographic, health characteristics, and urinalysis results. Logistic regression was used to evaluate the association of BMI categories with albuminuria. Linear regression analysis was applied to assess whether BMI, Ci, WC, WHt-ratio were independent predictor of HTN.

RESULTS

During WKD 2010 and 2011, n. 2209 and 2341 participants took part in the “School project”, respectively. Comprehensive data from 4550 students (2,486 females and 2,064 males) were evaluated both as a whole cohort, and divided on the basis of sex and 4 areas of our country – i.e. Northern, Central, Southern and Islands.

The characteristics of the population are reported in Table I. Coffee drinkers numbered 2,775 (61% of entire cohort; 1,228 females and 1,547 males); mean number of coffee per day was $1,82 \pm 1,04$. 1,288 were cigarette smokers (28,3% of entire cohort; 640 females and 648 males), males were heavier smokers (cigarettes per day: $8,17 \pm 4,8$) than females ($6,4 \pm 4,3$). Physical activities (55% of students) were performed more in males (1498) than females (1000). In both sexes, the main sport activities were: soccer (males 24,5% v.s. females 2,6%), gymnastic (males 27,9% Vs. females 35,8%), dancing (males 5,8% Vs.females 12,2%), swimming (males 9,1% Vs. females 10,9%) and volleyball (males 5,1% Vs. females 7,4%). (Tab II - III).

No differences in clinical characteristics and habits were found among the 4 areas.

Most students (89%) were conscious of the role and the function of the kidney. Interestingly, awareness of the words proteinuria (6,6%), chronic kidney

disease (70%), dialysis (65,3%) and transplantation (75,2%) was greatly increased compared to past editions of WKD. (Tab IV)

The main sources of information were parents (31%) and teachers (38%) but not general practitioners. (Tab V)

Almost all students were conscious of the importance of hypertension control and 62,2% of them had had a previous measurement of blood pressure; in previous editions 50% of the students had had blood pressure measured before.

4,4% of adolescents had last values of SBP and/or DBP more than 140 mm Hg and 90 mmHg respectively (Tab VI -VII). Incident HTN was found in n. 71 (1.6%) participants (n.32 female; n.39 male). ISH was present in 7,6% of students. In hypertensive participants (HP) median SBP and DBP were 144 mmHg (IQR:140-150) and 90 mmHg (IQR:90-94), respectively. Stage-1 HTN and Stage-2 HTN was present in 94.3% and 5.7% of HP, respectively. (Tab VIII) Overweight, class-I,II,III obesity percentage was 21.1, 10.1, 7.1, 1,4 in HP, respectively.

Compared to participants without HTN, HP had median: BMI=23.7(IQR: 21.9-27.8) Vs 21.8 (IQR:20.0-24.1), $p=0.001$ (Fig. 2); WC= 88.0 (IQR: 80.0-98.5) Vs 81.0 (IQR:74-89), $p=0.001$ (Fig.3); WHt-ratio: 0.50 (IQR: 0.46-0.59) Vs 0.47 (IQR:0.44-0.52), $p=0.001$ (Fig.4); Ci=1.22 (IQR: 1.16-1.31)Vs 1.21(IQR:1.14-1.29), $p=0.527$ (Fig.5). Multivariate linear

regression analysis showed that WHt-ratio was predictor of HTN ($p=0.02$) while WC was predictor of SBP ($p=0.001$).

Many students (74,2%) had undergone urinalysis before WKD as routine examination planned by their clinicians.(Tab.IX).

Urine dipstick was not performed in 10% of the cohort because of either refusal or concomitant menstruation.

At urine dipstick, proteinuria was present in 14,7%, leucocyturia in 14,5 %, hematuria in 8,6%. (Fig. 5) (Tab X).

The percentage of adolescents with normal weight was 73,1%, overweight 15,7%, class-I obesity 2,4%, class-II obesity 0,7%, class-III obesity 0,1%. Data pertaining to participants according to classes of BMI are shown in Table XI. In univariate analysis proteinuria was associated ($p=0.01$) positively to SBP and pulse pressure but inversely to BMI; no association was found with other variables. Leukocyturia and hematuria had not significant association with any other variables. In multivariable linear regression analysis no predictive factor was found among anthropometric indicators, urinary abnormalities and BP levels.

DISCUSSION

The aims of WKD was to the increase awareness, detection, prevention, and treatment of kidney diseases through a questionnaire, the measurement of blood pressure and dipstick urine test.

Most relevant information were acquired from the school project of WKD.

Despite the fact that many students were aware of the importance of blood pressure measurement, we found that only 62% of students had a previous blood pressure control. This finding demonstrates that this procedure has not yet been incorporated into the clinical practice. The result of another study (88) showed that only 28.6% of 1,215 brazilian students admitted had had their BP previously measured at home or another place (and not during a medical consultation).

Detecting high blood pressure at young ages is important for the control and prevention of hypertension in adulthood. The difficulty in performing this monitoring lies in the fact that adolescents, in general, do not know the values of their blood pressure for not measuring it routinely(89).

In our study we found 1,6% of new hypertensive students and ISH present in 7,6% of them without differences among the sex. Data also were confirmed in another survey(90) of WKD during years 2008-2009 in Italy. 3,939 students (1,901 females and 2,038 males) were evaluated and abnormal blood pressure was recorded in 225 participants (5.7%) and mostly in males (68%).

Early diagnosis of hypertension is very important in adolescents because it is considered a potential cardiovascular risk factor, when associated with the presence of early atherosclerotic lesions(91). Furthermore, high blood pressure in young populations progresses to hypertension in adults, especially among adolescents with a tendency to develop excess weight(92).

In a 15 years follow-up study, Bao(92) et al demonstrated that in 1505 individuals (56% female subjects, 35% black), aged 5-14 years, hypertension developed in early adulthood (at ages 20 to 31 years) was more prevalent in blacks, in subjects who had higher BP or BMI in childhood, or had gained more BMI from childhood to adulthood.

Evidence that hypertension is related to increases in body fat is well established in literature(93).

However, there are controversial opinions on their relationship with the distribution of body fat(94-95).

In a study(94) the levels of blood pressure and prevalence of high blood pressure were higher in overweight and obese adolescents (n = 912, age 13-17). In both genders, the prevalence of SBP and DBP increased directly correlated with increments in age, BMI and WC, although prevalence and odd ratios of high blood pressure were higher in individuals with increased WC in comparison to BMI.

To discriminate the amount of body fat and its distribution, gold standard are computed tomography or magnetic resonance but high costs of these methods limit their feasibility in clinical practice(96).

Actually anthropometric indicators have proven to be effective, especially in epidemiological studies with large samples. However, there are substantial differences between them. For instance the body mass index (BMI) might predict the overall fat but tends to overestimate the amount of body fat in adults with a high degree of muscle mass; the WC and the C-Index identify the fat located in the central region of the body; the C index is more widely used in research with adult populations(97-99). The WHtR considers the proportion of central fat by the individual's height. Furthermore, geographical difference has been observed in predictive value of anthropometric indicators; in fact WHtR has been regarded as reliable in predicting central fat and associated risk factors in Asian populations(100,101).

Beck(102) et al pointed out that all anthropometric indicators (BMI, WC, WHtR, C index) were good predictors for high blood pressure in adolescents (n=1642; mean age \pm SD:16.05 \pm 1.34).

By comparing the areas under the ROC curve of these four indicators, the C index presented a smaller discriminatory power than the others. Authors suggested the use of waist circumference to predict high blood pressure although the waist-to-height ratio and BMI have shown good areas under the ROC curve.

Instead we only found WC as a predictor of SBP and WHt-ratio as a predictor of HTN, confirming that the C-index is not a reliable predictor of HTN. Other studies in keeping with our study, demonstrated that, hypertension appeared to be significantly more frequent in adolescents with an abnormal WHtR (6.6 versus 16.1%, $P < 0.009$). This study is a part of the Sopkard programme, a comprehensive analysis of the overall health of 889 students, (428 girls, 461 boys) in the age range between 14 and 15 years with particular emphasis on the risk factors of lifestyle diseases, including metabolic syndrome, chronic kidney disease (CKD) and hypertension(103).

A survey in Greece found that WHtR and WC were more associated with cardiovascular risk factors than BMI(104), other studies have shown in a population of Chinese adolescents (range age: 12-19) that WC and BMI can be excellent indicators of clustering of cardiovascular risk factors (105,106) and that, when used together, can identify blood pressure variance, especially systolic blood pressure(107).

Evidence regarding the relationship of body fat distribution with cardiovascular risk factors in adolescents are not conclusive.

In the next step of our analysis, an attempt to search for a relationship between weight disturbances and albuminuria was made.

It is necessary to mention what was underlined by Jackson et al. that overweight adolescents have a 70% likelihood of remaining overweight or of developing obesity as adults (108).

In Italy, the presence of overweight and obesity was shown in 15.6% and 2,3%, respectively(109).

We found similar results in our study: overweight was observed in 15.7% of subjects and obesity in another 3,2% examined adolescents. Our cohort is representative of italian adolescents population.

In our students proteinuria was present in 14,7% without statistical differences both in normal weight subjects (14,8%) and in overweight (13,8%) / obese subjects (14,7%). There was no significant influence of overweight or obesity on the presence of albuminuria.

In contrast, Rutkowski(103) observed albuminuria in 16% of participants, but he pointed out that surprisingly proteinuria appeared to be more often in Polish adolescents with normal weight. The National Health and Nutrition Examination Survey (NHANES), a population-based study including 2,515 adolescents, reported a albuminuria prevalence of 0.3% in overweight adolescents compared to 8.7% in non- overweight ones (110). According to authors a possible explanation for this finding is that normal-weight children are more likely to exercise 24 h prior to urine collection, leading to physiological microalbuminuria(111). Anthropometric indicators, urinary abnormalities and BP levels were not predictor of presence of proteinuria.

Similar to our results, Radhakishun(112) and coll reported albuminuria was not associated with any of the cardiometabolic risk factors assessed.

In the adolescents population, however, data from longitudinal studies assessing the cardiovascular morbidity and mortality in healthy and obese children with albuminuria are lacking. Although studies show conflicting results with respect to the association between albuminuria and cardiometabolic risk factors, associations with insulin resistance, hypertension and dyslipidemia have been reported in obese adolescents(110,113).

The pathophysiological mechanisms underlying the association between albuminuria and obesity are not fully understood. Another hypothesis is that insulin interferes at several points in the renin–angiotensin–aldosterone system, increasing its activity despite a state of sodium retention and volume expansion(114). Through this route, reduced insulin sensitivity (leading to higher plasma insulin levels) may lead to vascular damage and renal injury(114). The most likely explanation for this phenomenon is that a longer exposure to obesity and insulin resistance is needed before any impairment of renal function develops. This problem needs deeper analysis and future investigations.

There are several limitations to our study. A single urine specimen may be subject to random variation and transient proteinuria from prolonged standing

or exercise(115); however, single-measure albuminuria does reflect a chronic condition in 63% of the general population(116). Urine was collected at any time during the day, whereas first-morning midstream urine may be preferred for albuminuria assessment and urinalysis(117,118).

Urinary measures and blood pressure were evaluated only at the WKD visit, we do not have other confirmation data and further evaluation done after the survey in the presence of an abnormal urinary dipstick and/or blood pressure result.

This study also lacked some clinical attributes, such as serum creatinine and GFR; however, self-reported hypertension and diabetes were available, and measured glycosuria may indicate undiagnosed or undertreated diabetes.

Despite these limitations, this study represents a large sample of young adults in the Italy, and the lack of association between albuminuria and anthropometric indicators is particularly interesting.

The guidelines from the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) recommend screening for albuminuria among people who are at risk for kidney disease, including those with established diabetes or hypertension, other systemic illnesses, family history of kidney disease, and age 60 yr (119). Obesity is not mentioned but might be a novel candidate screening criterion.

Other studies are necessary to understand the role of routine measurement of albuminuria in asymptomatic overweight and obese adolescents.

CONCLUSION

School project of WKD is an important survey to the prevention of kidney diseases in young adolescents. Overweight and obesity are present in a significant percentage of our students. This phenomenon is strictly connected to the presence of HTN in our populations: WHt-ratio is significantly associated to the presence of HTN and WC is associated to levels of SBP. Independent from these factors, also albuminuria is quite often present in adolescents and it is associated with SPB and pulse pressure but not with anthropometric indicators. A prospective study of the relationship between anthropometric indicators and early markers of kidney damage in young adults is warranted.

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TABLES AND FIGURES

Fig. 1. WKD Topics

Year	Topic
2006	Are your kidneys OK?
2007	CKD: Common, harmful and treatable
2008	Your amazing kidneys
2009	Protect your kidneys: Keep your pressure down
2010	Protect your kidneys: Control diabetes
2011	Protect your kidneys: Save your heart
2012	Donate – Kidneys for life - Receive
2013	Kidneys for Life – Stop Kidney attack
2014	Kidney Health for All

Tab. I Clinical Characteristics

	Female (N. 2,486)	Male (N. 2,046)	P value
Age (Year)	18 ± 1	18 ± 1	NS
SBP mmHg	113,2 ± 13,1	120,7 ± 14,1	0,01
DBP mmHg	69,5 ± 9,1	71,1 ± 8,9	0,01
Smokers (%)	25	31	NS
Coffee drinkers (%)	49	74	0,01
Weight (kg)	58,9 ± 11,6	72,4 ± 9,9	0,01
Height (m)	1,6 ± 0,1	1,7 ± 0,1	0,01
BMI (kg/m²)	21,8 ± 3,3	23,1 ± 3,3	0,01
WHtRatio	0,4 ± 0,05	0,4 ± 0,06	0,01
WC (cm)	79,8 ± 10,7	84,9 ± 10,5	0,01
C index	1,2 ± 0,1	1,2 ± 0,1	NS

Data are expressed as means ± SD, or percentage.

SBP: Systolic Blood Pressure

DBP: Diastolic Blood Pressure

Tab.II Physical Activities

	Female (n.1000)	Male (n. 1498)
GYMNASTIC	35,8	27,9
TENNIS	1,3	1,5
VOLLEYBALL	7,4	5,1
MISCELLANEA	4,7	5,8
BASKET	0,8	3,0
BODY BUILDING	0	1,2
DANCING	12,2	5,8
JOGGING	3,7	3,0
BOXING	1,1	1,4
FOOTBALL	2,6	24,5
SWIMMING	10,9	9,1
ATHLETICS	1,1	1,4

Data are expressed as percentage (numbers).

Tab III. Physical Activity Intensity

		Female	Male
Training	Mean ± SD	2,32 ± 0,918	2,53 ± 0,925
	Median	2,00	3,00
	Minimum value	1	1
	Maximum value	5	5

Tab. IV Responses to Questionnaire

	N.	%
Awareness of kidney's role in body regulation	(4064)	89,53
Awareness of chronic kidney disease	(3005)	70,6
Awareness of the meaning of term <i>proteinuria</i>	(301)	6,6
Awareness of dialysis	(2811)	65,3
Awareness of kidney transplantation	(3175)	75,2
Previous urine analysis performed	(3375)	74,2
Previous measurement of blood pressure	(2640)	62,2

Data are expressed as percentage (numbers).

Tab. V Information Sources

	N.	%
Parents	(864)	31,0
Teachers	(1073)	38,5
Medical Doctor	(192)	6,9
Friends	(127)	4,6
Newspaper	(44)	1,6
TV	(136)	4,9
INTERNET	(61)	2,2
Patient	(176)	6,3
Other	(108)	3,9

Data are expressed as percentage (numbers).

Tab. VI Previous Known HTN

	N.	%
Normal < 140/90 mmHg	(774)	95,7
HTN	(7)	0,9
ISH	(28)	3,5

HTN: Hypertension

ISH: Isolated Systolic Hypertension

Data are expressed as percentage (numbers).

Tab VII. Previous Known Blood Pressure Values

	SBP	DBP
Mean ± SD	115,3 ± 12,84	71,33 ± 9,39
Median	120	70
Minimum value	70	30
Maximum value	173	100

SBP: Systolic Blood Pressure

DPB: Diastolic Blood Pressure

Tab. VIII Incident HTN

	N.	%
Normal < 140/90 mmHg	(4479)	90,8
Stage 1 HTN	(67)	1,5
Stage 2 HTN	(4)	0,1
ISH	(345)	7,6

Data are expressed as percentage (numbers).

HTN: Hypertension

ISH: Isolated Systolic Hypertension

Fig. 2: Association between SBP and BMI in total cohort of students

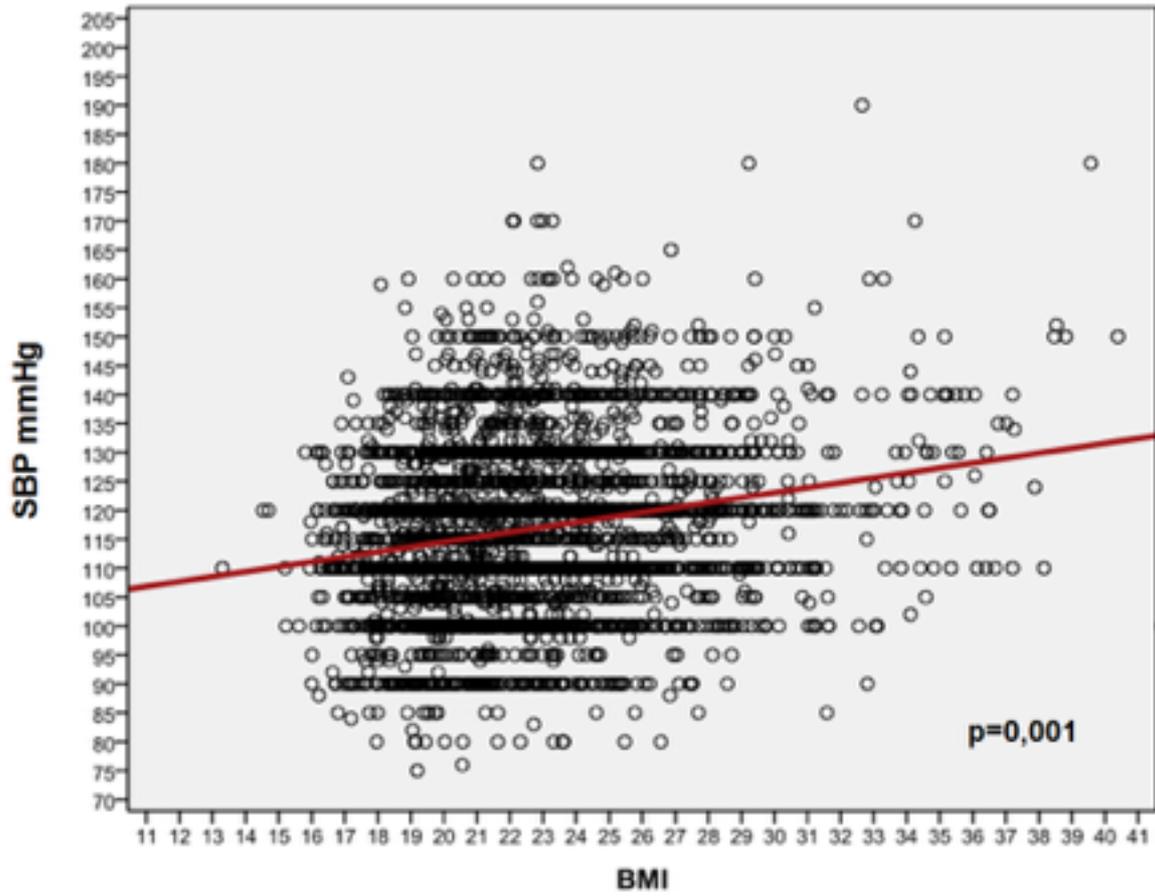


Fig. 3: Association between SBP and WC in total cohort of students

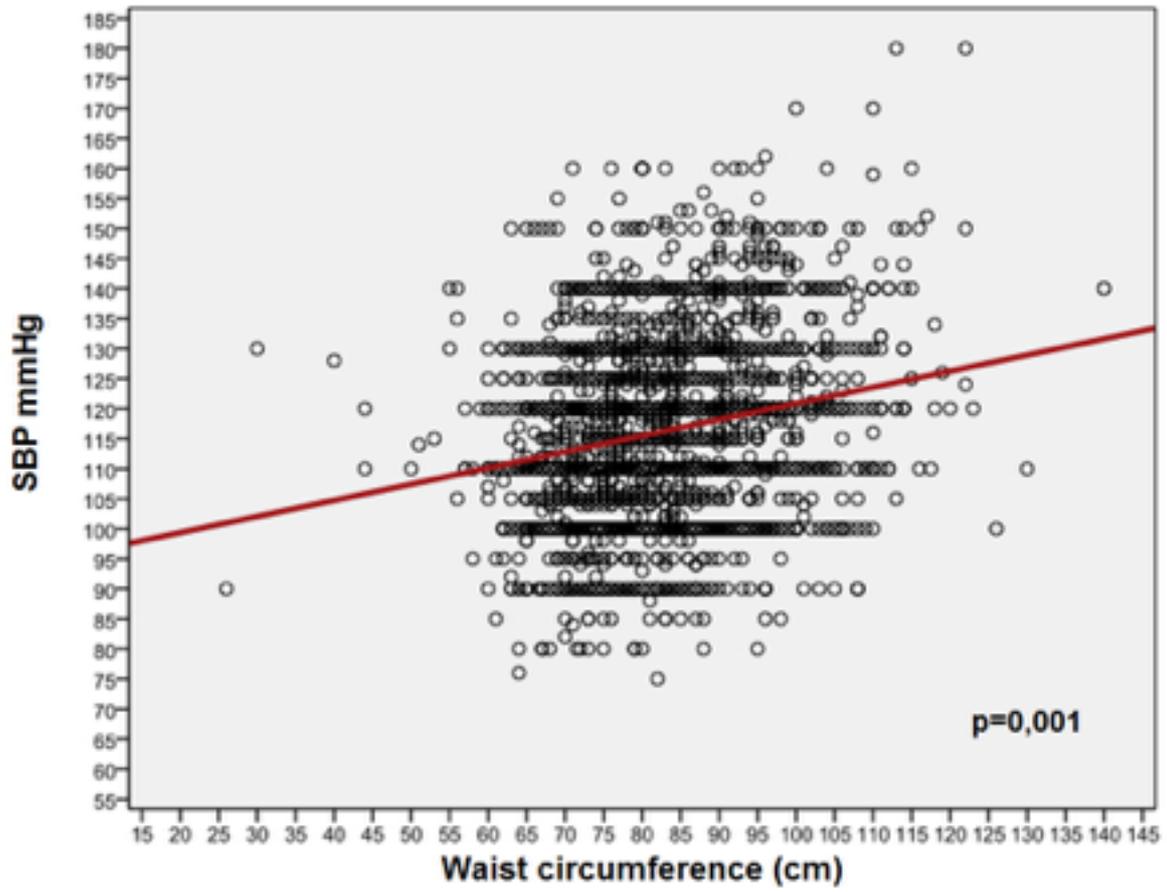


Fig. 4: Association between SBP and WHtRatio in total cohort of students

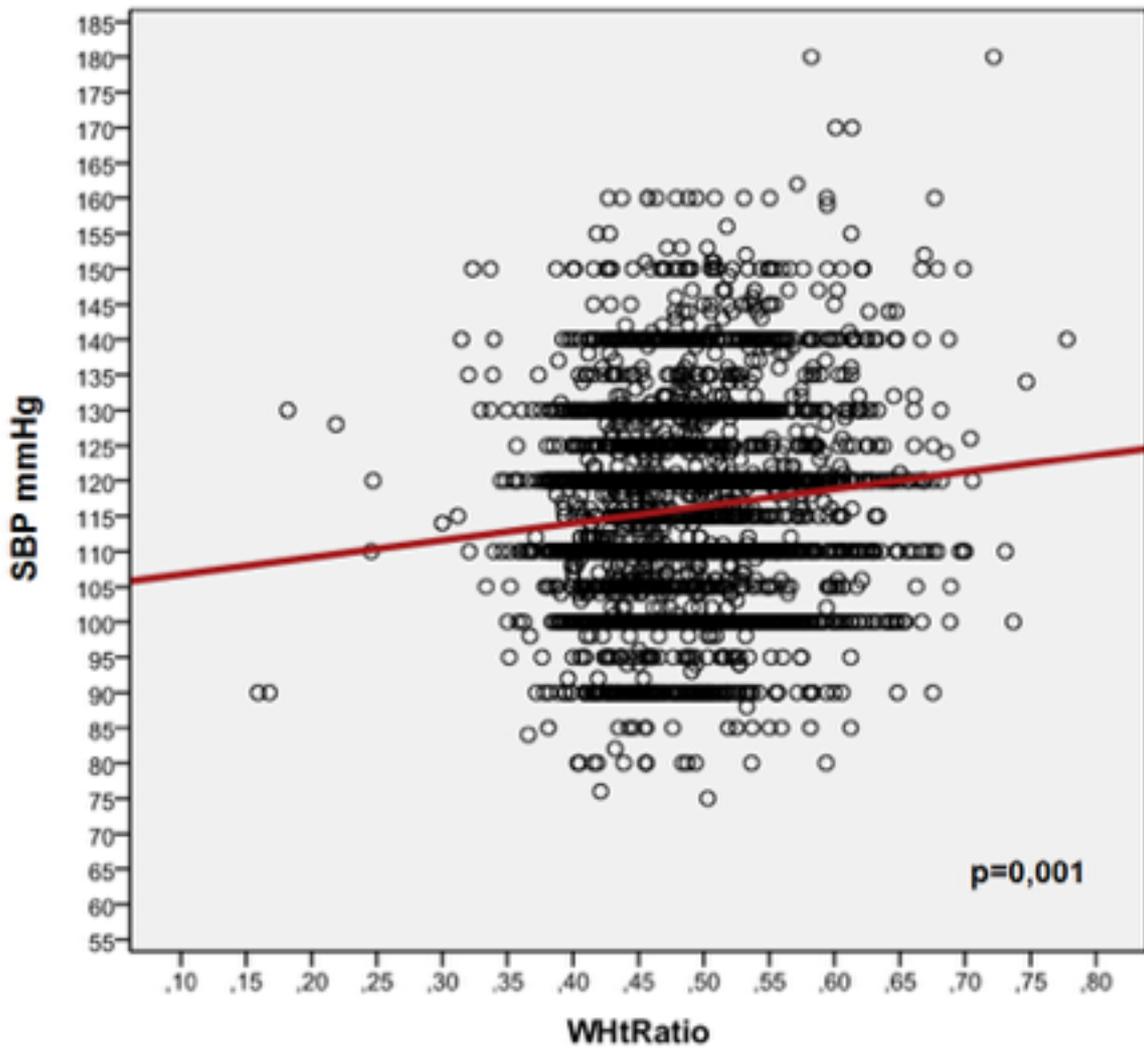
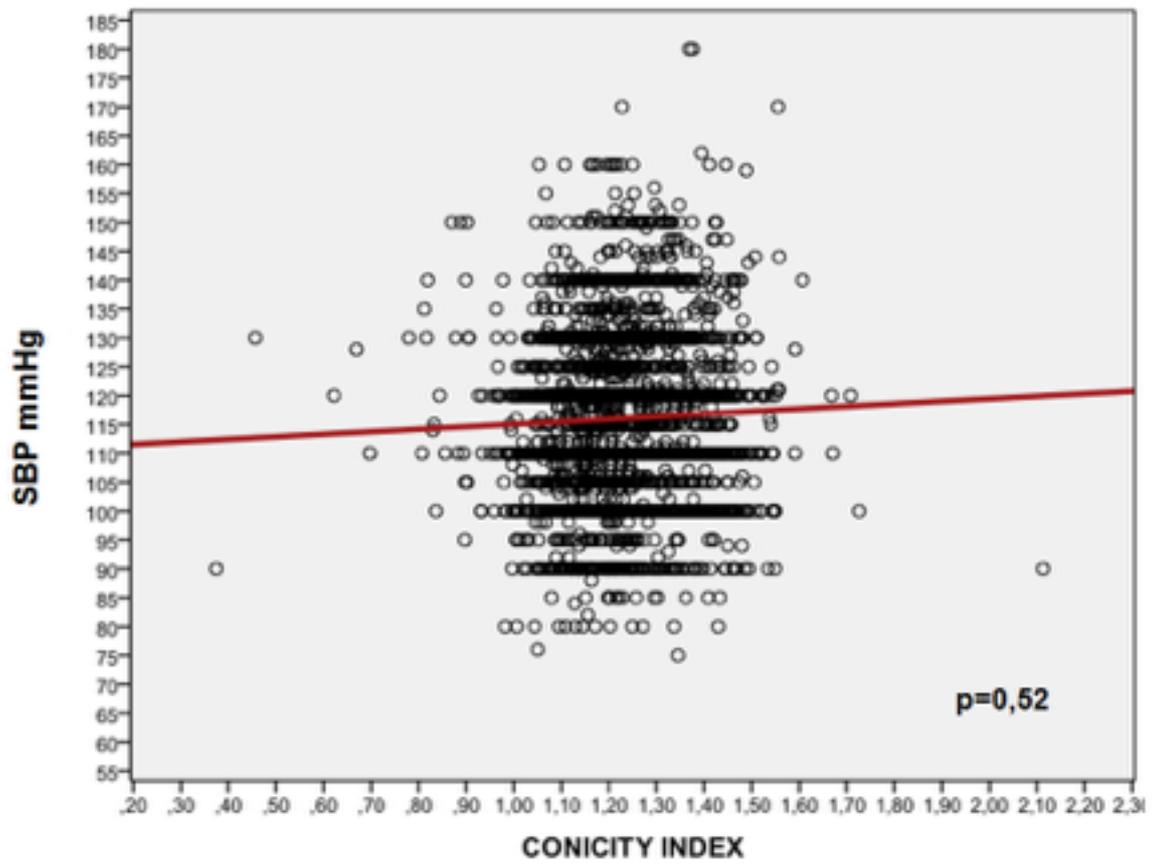


Fig. 5: Association between SBP and Conicity Index in total cohort of students



Tab. IX. INDICATION FOR URINALYSIS

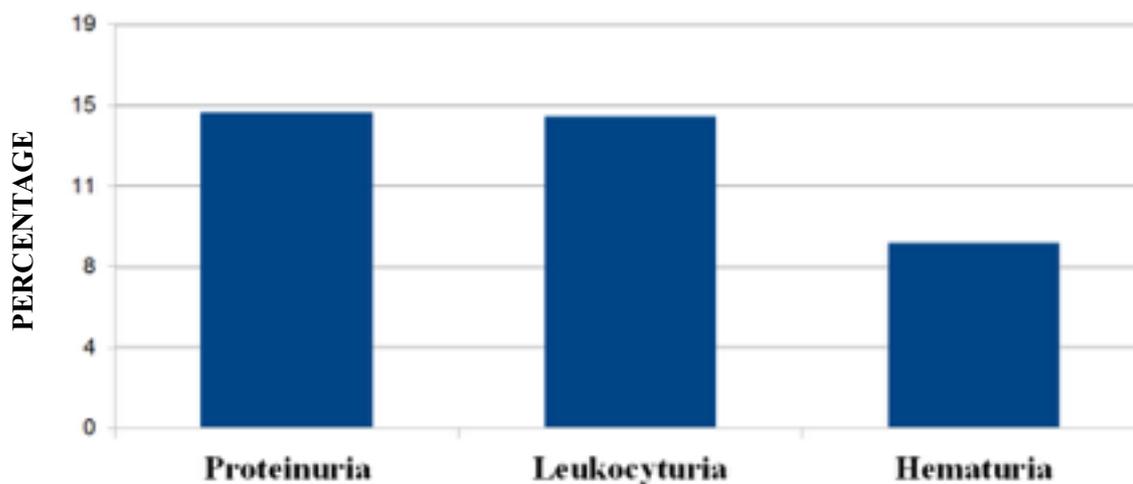
	N.	%
ROUTINE ANALYSIS	(2079)	45,7
DONT' REMEMBER	(4)	0,1
EVALUATION FOR SPORTS	(473)	10,4
PAST CYSTITIS	(98)	2,2
RENAL STONE	(15)	0,3
SURGERY	(54)	1,2
MISCELLANEA	(25)	0,5

Data are expressed as percentage (numbers).

Tab X. Dipstick Results

		Leucocyturia mg/dl	Glicosuria mg/dl	Proteinuria mg/dl
Female	Mean	139,8	50,0	29,1
	± SD	166,5	0,2	41,9
Male	Mean	50,2	50,0	32,7
	± SD	73,9	0,4	70,8
P value		0,01	NS	NS

Fig. 6: Dipstick Results in total cohort of students



Tab. XI: Hypertension and urinary abnormalities according to BMI class

BMI	HTN	ISH	Proteinuri a	Glicosuria	Leucocyturia
Normal-Weight (Mean ± SD)	1,3 %	6,8 %	30,3 ± 61,7	50 ± 0,1	123,1 ± 160,0
Overweight (Mean ± SD)	2,2%	11,8%	25,0 ± 35,7	50 ± 0,3	127,8 ± 156,5
Obesity Class I (Mean ± SD)	6,5%	19,4%	33,2 ± 35,7	50 ± 0,7	122,5 ± 157,4
Obesity Class II (Mean ± SD)	16,1%	32,3%	57,5 ± 60,1	50 ± 0,4	25,0 ± 0,1
P value	0,01	0,01	NS	NS	NS

HTN: Hypertension

ISH: Isolated Systolic Hypertension

BMI: Body Mass Index