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IFCC Professional Scientific Exchange Programme Report - BIOCHEMICAL MARKERS OF BONE TURNOVER

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Mrs. Cekovska visited for 2 months (June-July 2000) as an IFCC scholar the Dept. of Clinical Biochemistry and Laboratory Medicine (Head: Prof. Dr. W. Jaross), Medical Faculty Carl Gustav Carus, Dresden, Germany. She was trained by Drs. S. Bergmann and Gerish.

Introduction

The processes of bone formation and resorption, known as 'bone remodeling', are continuous throughout life and are necessary for the maintenance of a normal functional skeleton. Bone formation by osteoblasts results from the synthesis of matrix followed by mineralisation, whereas resorption by osteoclasts involves matrix degradation and dissolution of the mineral phase. These two processes are very tightly coupled, so that when a specific amount of bone is degraded, the same amount is formed to replace it. Prolonged excess of bone resorption over formation results in loss of bone, and hence in development of osteoporosis.

Beside techniques for measuring bone mineral density, the biochemical markers of bone turnover, have a large potential for early diagnosis of osteoporosis and other endocrine and metabolic bone diseases, such as hyperparathyroidism, Paget's disease, thyroid disorders, multiple myeloma, renal insufficiency, metastatic bone disease, drug-induced bone loss etc. There are a number of biochemical markers of bone turnover currently in use: bone-alkaline phosphatase (b-ALP) and osteocalcin as markers of bone formation, pyridinoline-cross links (PYD), desoxypyridinoline-cross links (DPD) and cross-linked N-telopeptides of type I collagen (NTx) as markers of bone resorption.

My attention was particularly concentrated on immunoassays for measuring urinary excretion of PYD and DPD as markers for monitoring bone resorption. These parameters will be of main interest to me in my future professional work. The pyridinium derivatives (DPD and PYD) are both non-reducible crosslinks that are derived from lysine and hydroxylysine residues in mature collagen and elastin. DPD is present only in type I collagen of bone and is very specific measure of bone resorption. PYD is also found in type II collagen of cartilage, but because of the comparatively larger mass of bone collagen and the slower turnover rate of cartilage collagen, most PYD excreted in the urine originates in bone. Measurement of PYD and DPD is intended for use as an aid in monitoring bone resorption changes in postmenopausal women receiving hormonal or biphosphonate antiresorptive therapies and in individuals diagnosed with osteoporosis. Osteoporosis is one of the main complications of the postmenopause.

Methods and Probands

During my work in the host laboratory, I received practical training in the techniques for measuring these markers: serum b-ALP (wheat germ lectin precipitation method, Roche), serum osteocalcin (chemiluminescence assay, Nichols Institute Diagnostics), urinary NTx (enzyme-linked immunoassay, Osteomark®), urinary PYD crosslinks (enzyme immunoassay, Metra Biosystems), and urinary DPD crosslinks (enzyme immunoassay, Metra Biosystems). I gained practical experience in assay performance and assay standardization, as well as knowledge about pre-analytical, analytical variability and biological variability (which include physiological changes, such as diurnal, menstrual and seasonal rhythms, changes with menopause and aging, as well as somatic growth).

With aim to identify women who have abnormally high bone turnover we measured the urinary excretion rate of pyridinolines (Metra Biosystems immunoassays) in middle-aged women. PYD and DPD were measured in the second morning urine of 304 middle aged women (40-65 years) without known osteoporosis. For normalization of urinary pyridinolines urine creatinine was measured.

Results

The first subgroup included 112 premenopausal (pre-M) women, 34 with current use of oral contraceptives (OC). 82 women were in the perimenopausal age, 48 of them with a preventive use of hormone replacement therapy

Groups	PYD nmol/mmol crea		DPD nmol/mmol crea	
	Mean	SD	Mean	SD
PRE-M	26,6	6,88	6,08	2,05
PERI-M	29,8	8,71	6,81	2,76
PERI M with HRT	25,69	8,41	5,54	0,77
POST-M	37,46	10,18	7,77	3,06
POST-M with HRT	26,97	8,07	5,40	1,83

tory, I received practical and theoretical training in the techniques for measuring several biochemical markers of bone turnover. I wish also to express my gratitude to Dr Bergmann and Dr Gerish and all the staff in the hormonal laboratory and laboratory for DNA analysis for giving me practical help and precise direction to broaden my personal knowledge related to bone markers.

Table 1: Urinary Pyridinoline-cross links (PYD) and Desoxypyridinoline-cross links (DPD) in pre-, peri- and postmeno-

(HRT). The group of postmenopausal (post-M) women consisted of 120 women (47 after surgical menopause, 27 with a postmenopausal HRT). Pre-M women were five years younger than peri-M and eight years younger than post-M. Results obtained from the pyridinoline-links assay must be corrected for variations in urine concentration by dividing the pyridinium crosslinks value (nmol/L) by the creatinine value (mmol/L). The excretion rate of PYD varied between 8.2 and 194 nmol/mmol creatinine, that of DPD between 0.7 and 39.2 nmol/mmol creatinine. Our results (table 1) have showed the lowest values for both parameters among pre-M women using OC (there was no difference between premenopausal women using OC and those who did not) and the highest among post-M women without HRT. Differences between pre-M women with and without use of OC were not significant. A postmenopausal HRT was able to lower excretion of both PYD and DPD significantly. In contrast, a preventive use of HRT in the perimenopausal age had no effect on urinary excretion of pyridines. The results from our study confirmed the utility of PYD and DPD measurement for identifying individuals with increased bone turnover and for monitoring bone resorption changes in postmenopausal women receiving hormone replacement therapy.

The reference values for Urinary Pyridinoline-cross links (PYD) and Desoxy-piridinoline-cross links (DPD) are given in table 2.

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I owe great gratitude to my host Prof.Dr. Werner Jaross for his generosity in giving me useful advises concerning my stay and work in Dresden. This enabled me to come back home rich with knowledge necessary for my future professional activity. During my work in the host labora-

Groups	PYD nmol/mmol crea		DPD nmol/mmol crea	
	Median	90 th percentile	Median	90 th percentile
premenopausal	25,3	34,9	5,3	7,8
perimenopausal	27,5	43,1	6,8	10,5
postmenopausal without HRT	35,6	53,3	7,1	11,6
postmenopausal with HRT	25,9	33,1	5,3	7,9

Table 2

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