cases, whereas it is 1-2% in families with one case only. However, in a study that has been held in Turkey since 2012 in a series of 51 MPHD cases, sequence analysis of the *PROP1* gene was performed and one case and the affected brother were found to have homozygous 'stop' codon and other cases were found to have no mutations. *POU1F1* gene is necessary for the change and permanence of thyrotroph cells, somatotroph cells and lactotroph cells. The gene can both show dominant and recessive inheritance and also the heterozygous mutations, which can result in disease and cause a function loss in the gene product by dominant negative effect. Between 2007 and 2009, a project entitled 'the analysis of *PROP1, PIT1, HESX1* and *LHX3* mutations in multiple pituitary hormone deficiencies' was carried in nine Pediatric Endocrinology Clinics from Turkey with cooperation of İstanbul University Pediatric Endocrinology Clinic and Medical Genetics Department. The aim of this project was to investigate the mutations in the *PROP1, PIT1, HESX1* and *LHX3* genes which are unique to the Turkish population, to examine the relationship between phenotype and genotype, to evaluate the contribution of these mutations to early diagnosis and treatment and to complete the preliminary studies in indication of new genes in cases and families which are found to have no mutations. In 55 cases, 38 sporadic and 17 familial, clinical examination, hormone values, neuro-radiologic evaluation and pedigree were completed. The DNA samples from cases and their families have been kept in a bank. Firstly, DNA sequencing method and secondly, the multiplex ligation-dependent probe amplification (MLPA) procedure, for investigation of all gene/exon deletions in related genes in cases that were found to have no mutations, have been performed as molecular study gradually. A mutation was determined in total of 30.9% of cases: in 21.8% of cases-*PROP1* mutation, in 7.3% of cases-*POU1F1* mutation and in 1.8% of cases-*HESX1* mutation. In this study, one new mutation in the *PROP1* gene and three new mutations in the *POU1F1* gene were identified. The 66% of the mutations present in *PROP1* gene were whole gene mutations and this result showed the contribution of MLPA test to diagnosis in molecular genetics approach.

Key words: Genetics, pituitary, short stature

Clinical Findings of Osteoporosis

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Osteoporosis is one of the skeletal diseases which result in increase of fracture risk because of declined bone strength. In these days, it is necessary to evaluate osteoporosis as a disease related to multiple genetic, physical, hormonal and nutritional factors. Bone strength has two major components: 1) Bone density and 2) Bone quality. Osteoporosis causes fracture formation with minimal traumas during daily activities. The loss of bone density and deterioration of bone quality is an inevitable consequence of aging. In women, trabecular bone loss accelerates after menopause. With aging, the plaques forming vertebrae attenuate and the connections between trabeculae decrease. Moreover, horizontal trabeculae decrease more than the vertical trabeculae. The most important result of osteoporosis is fractures and most important of those is hip fractures. All around the world, as the number of old population increases, the incidence of hip fractures also increases. The prevalence of osteoporosis increases with the aging population, as well. Over age 50, one in every four women and one in every 8 men are found to be osteoporotic. Again, every white woman over age 50 has 40% risk of fracture in the hip, vertebrae, or wrist. The prevalence of vertebral fracture in postmenopausal women is estimated to be 20%. As a result, fractures related to osteoporosis can be seen in one in every two women and one in eight men in Caucasians. For indicating how dangerous osteoporosis is, one in every six women pass though the risk of hip fractures, whereas one in every 9 women has the risk of catching breast cancer. Besides, the mortality of hip fracture is way higher than the mortality of breast cancer. 50-60% of patients passing through a hip fracture cannot reach their previous functional capacity and 20% of those need long-term care. Along with the high mortality and morbidity rates of fractures depending on osteoporosis, they also bring an enormous economic burden on countries. Merely one third of osteoporotic patients get the right diagnosis, solely one seventh of osteoporotic patients get the right treatment.

More than one factor should be taken into consideration in the development of osteoporosis and these are:

1) Peak bone mass: the maximum bone mass reached at ages 25-30.

2) The rate of bone turnover.

3) The micro-architecture of bone and bone quality: The differences occurring in organic matrix of bone.

4) The macro-architecture of bone: the massiveness of bone, the length of femur and the ratio of the periosteal bone formation over endosteal bone turnover.

Peak bone mass essentially identified genetically. The determinants of bone formation are heredity, gender, nutrition (calcium and protein intake), endocrine factors (sex steroids, calcitriol, insulin-like growth factor-1), physical activity and having a particular body mass index. Osteoporosis occurs as a result of either pause in bone formation or increase in bone resorption. In menopause, the main reason behind the fast bone resorption is lacking of estrogen. The bone resorption is fastest in the first 5-10 years of menopause. After that, decline in the bone mineral density (BMD) gets slower but it continues through the life span. With the perforation and the loss of trabeculae, an irreversible damage occurs in micro-architecture of bone. Moreover, other factors increasing the bone resorption are also important. The BMD is lower in heavy smokers. The relative risk of hip fracture in tobacco users is said to be 1.2-1.5, because tobacco causes the circulating estrogen to be inactivated immediately. Alcohol consumption is also important for fracture risk both in women and men. Alcoholism generally leads to nutritional deficiency, weakness, liver diseases, malabsorption, vitamin D deficiency, hypogonadism, hemosiderosis, parathyroid dysfunction and bone resorption. The bone density differs among the races. The fundamental reason for less hip fraction rates in dark race is their higher bone mass. In all races, there is a correlation between body mass index and BMD. Both fatty and non-fatty body mass could have a positive effect on bone mass. Obesity is a protective factor against osteoporosis. In this case, the mechanical load on bones and the estrogen synthesis in fat tissue has a positive effect. The intake of calcium has important effects on reaching peak bone mass and the protection of bone mass in elderly. The most feared complication of osteoporosis in elderly is the fractures in the hip, vertebra and wrist. The fractures usually occur because of falling down after a balance problem. Besides, vertebra fractures can occur during daily activities and without any fall. The presence of a fragility fracture in a patient's history is an important evidence of osteoporosis. Fragility fracture is a trauma with a very low energy which normally would not create a bone fracture.

In reality, bone fractures are dependent on two factors:

1) Trauma

2) Personal risk factors

Here, neuromuscular coordination, balance and sight problems come into the question. BMD can be accepted as one of the personal factors. BMD, can give an idea about the strength of the bone as a whole. Age and gender become important matters in rise of osteoporotic fractures. A progressive disruption occurs in trabecular micro-architecture of bone with aging. The most evident findings are the separation of trabeculae and plaque perforation with the decrease in trabecular number. No different structures are established depending on different genders. On the contrary, women tend to have more horizontal trabeculae perforation than men. This feature explains why there are more vertebral fractures in women than men. Because the gonadal functions decline later in men compared to women, the bones are better protected in men than women. As a result, the largeness of bones, the higher cortical bone density after age 55 and the slower loss of trabecular bone provide more durable bones in men than in women. Various studies showed that the previous bone fractures increase the risk of consequential fractures. After the first vertebral fracture, the risk of following fracture can rise up to 3-5 times. Presence of a fracture in a bone may be a result of structural deformities. The damages, which could probably not be shown in BMD measurements but could likely be present in skeletal micro-architecture, make the bone more fragile. General health situation, prescribed drugs and having another disease increase the risk of fractures by 2.6 times. Drugs like benzodiazepines affect the risk of fractures by increasing the number of falls.

Clinical Findings of Osteoporosis: Like in every patient, the history of the patient should be taken, after that physical examination should be done and biochemical survey should be completed; at the end, the definitive diagnosis and the most appropriate treatment modalities should be determined. Unfortunately, the ultimate finding of osteoporosis is fracture. The most serious fracture site is hip, however, wrist and vertebral fractures can result in critical pain, deformity and limitation of movement. The fractures after age 50 without any serious trauma should bring the osteoporosis in mind. There is a very long subclinical period for osteoporosis. During this period, patients do not have any complaints or do not show any symptoms. The first symptom is usually back pain. Sometimes, this pain would start suddenly, without any sign. It can be severe. It usually appears after some heavy weight has been carried. The character of pain is usually sharp and burning and it increases as some heavy load has been carried around or with motion. This situation appears usually when there is a compression fracture. 12th thoracic or 1st lumbar vertebrae are the ones mostly affected. After the fracture heals, the pain fades away. Depending on the paravertebral muscle spasm, the obtuse pain can continue for some time. Dorsal kyphosis (widow's hump), shortening and deformities as a result of recurring vertebrae fractures are typical findings. For a normal person, height and arm span are equal where as in patients with osteoporotic fractures, heights gets shorter compared to arm span. In severe cases, lower ribs can lean on iliac bone. However, before relating the severe pain to osteoporosis, systemic and local causes of pain should be investigated broadly. As a result of fragility in severe osteoporosis, a trauma with a low energy, which would not create any fracture in a normal person, could cause a fracture in these patients.

It should be always kept in mind that various kinds of serious diseases could cause osteoporosis. Therefore, especially when a doctor encounters a man or a premenopausal woman with osteoporosis, secondary osteoporosis causes should be investigated at first place. Pain, deformities, decline in activity, decrease in life quality, permanent disability and death can occur as a complication of fractures. Moreover, as a result of deformities, the risk of formation of restrictive lung disease should be considered.

Osteoporosis diagnosis: There are lots of factors, related or not to the skeleton, defining the fracture risk. However, between these factors, most important one is the condition of bone mass. Bone mass measurements (BMM) are the most important parameter in both diagnosing osteoporosis and also calculating the risk of fracture. Every 1 standard deviation (SD) decrease in BMM increases the risk of fracture by two times. Thus, every person with osteoporosis has the four times increased risk of fracture. According to the World Health Organization's criteria, the BMD of the patient should be compared to the normal person's BMM at the same age and gender. The measured T-score of the patient defines how much SD below compared to normal young population is one's BMD. Osteopenia is defined as a T-score between -1.0 and -2.5 and osteoporosis is defined as a T-score of -2.5 or below. Severe osteoporosis is defined as T-score below -2.5 together with presence fragility fracture. For old people with osteoporosis, the vertebral measurements would give false results. The foreseeing of the fracture risk of a specific region in the skeletal system would optimally be obtained by the BMM of that specific region. During menopause, wrist, hip and vertebra measurements are valuable, whereas in elderly, because hip fractures matter more, femur BMM is more valuable.

Osteoporosis cannot be recognized with a plane radiograph before the bone loss is above 25-40%. However, still the anteroposterior radiographies of thoracic and lumbosacral vertebrae should be done. The most important finding in radiographies is the deformities in vertebrae. Echogenic last plaques, increase in vertebral trabeculation can be present. Codfish vertebra sign is the finding of a severe osteoporosis. The compression fracture should be identified. Conventional radiologic techniques can be used to differentiate osteomalacia, primary hyperparathyroidism and metastatic lesions. Compression fractures on 6th thoracic vertebrae or the compression fracture with a severe collapse in the back of vertebra column would make the doctor think about a malignant metastasis. For differential diagnosis bone scintigraphy can also be beneficial. Before diagnosing with primary osteoporosis, all of the causes of secondary osteoporosis should be excluded. To exclude secondary osteoporosis, extensive clinical and laboratory techniques are needed. Hemoglobin, leukocyte and leukocyte formula, as well as sedimentation are useful for exclusion of malignant diseases. Urine tests, acid-base evaluation, calcium, phosphorus, alkaline phosphatase, intact parathormone, fasting blood sugar, creatinine, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, serum and urine electrophoresis, serum 25-hydroxy vitamin D levels, thyroid-stimulating hormone, free triiodothyronine, thyroxine, luteinizing hormone, follicle-stimulating hormone, prolactin, plasma testosterone and estradiol levels, urine cortisol or 1 mg dexamethasone suppression test, calcium levels in 24 hour-urine test can be done for necessary patients.