Observations on Osteoporosis in Three Generations of Descendants of Holocaust Survivors

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ABSTRACT: Throughout history, studies on episodes of famine have led to the discovery of metabolic abnormalities and hormonal aberrations as well as an increased incidence of cancer and mental health conditions. Starvation during early life is thought to influence the programming of childhood and adult bone metabolism, which may result in poor bone health in later life. This observational case series includes a small group (with no control group) of famine-exposed Holocaust survivors and their descendants. We proposed a mechanism to determine any association between starvation and osteoporosis, both in the individual survivors and in their descendants.

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Famine, as a socioeconomic phenomenon, has occurred throughout history. By the 20th century food production had reached an all-time high, with levels sufficient enough to feed the entire world population. Nevertheless, due to political and environmental factors, famine has occurred regularly despite food availability. There was widespread famine across multiple countries during World War II and more than 75 million people perished as a result of nutritional deprivation [1].

STARVATION DURING WORLD WAR II AMONG THE JEWISH POPULATION

The medical conditions of people exposed to starvation during the Holocaust and World War II have been widely studied. The Nazi regime imposed famine not only on the Jewish population but also on other groups. Studies investigating the metabolic changes in the survivors of famine from many areas, including European countries (Sweden, Netherlands, and England), Russia, and China, have been conducted. These studies have investigated bone mineral metabolism, metabolism of glucose and lipids, hormone secretion, and malignancy. Results of these studies have found that starvation in utero or in early childhood is associated with premature adult disease, including osteomalacia and osteoporosis [2,3].

The relationship between osteogenesis and osteolysis and the ill effects of malnutrition have been previously studied [4-6]. In two studies based in Israel, a connection between increased risk of osteoporosis in survivors of the Holocaust and osteoporosis has been identified [7,8]. In this present study, we evaluated the descendants to determine whether bone mineral metabolism was affected differently due to starvation, compared to lipid and glucose metabolism.

The aim of this paper was to re-emphasize the effects of starvation on the first generation of survivors, to raise awareness of the possibility of early osteoporosis in the second and third generations, and to encourage researchers to expand their range of study to include a larger number of survivors and their descendants.

PATIENTS AND METHODS

Survivors of the Holocaust (n=4) as well as their second (n=17) and third generation descendants (n=5) were included in this case series. The survivors had been exposed to starvation and/or malnutrition of varying degrees. Some had been hidden from the occupying forces during WWII. Others were interned in ghettos or incarcerated in concentration camps maintained by Nazi Germany [9-11].

We conducted detailed clinical investigations based on internationally recognized criteria, including bone densitometry. Cases were assessed based on the Garvan Fracture Risk Calculator (Garvan Institute, Sydney, Australia), which is an algorithm that includes input of clinical criteria, the history of falls, the age at which fractures occur, and T scores or densitometer (DEXA) readings [12].

We compared results from the calculated Garvan risk with the Sheffield FRAX test, which emphasizes bone mineral density (BMD), height, weight, and T score or Z score, calculated over 10 years for hip or general skeletal fracture risks [13]. All patients treated with pharmaceutical agents or cases involving additional extraneous factors were excluded from the study. These criteria included any cases affected by viral infection, alcohol intake, nicotine or opioid use, anti-metabolites, radiation, pharmaceuticals such as thalidomide (in limb development), diethylstilbestrol (DES) for malignancy, folate deficiency for spinal malformations, and lack of vitamin K during the first trimester of pregnancy, which could predispose the fetus to cerebral hemorrhage if the mother is taking anticoagulant therapy [Figure 1].

RESULTS

FIRST GENERATION: THE SURVIVORS

All first generation survivors were identified from the author's private practice and diagnosed < 70 years of age. Many similar cases were identified but were not scientifically diagnosed as the technology was yet not available. Only patients for whom full documentation was available were included in Table 1.

SECOND GENERATION: CHILDREN OF SURVIVORS

A group of 17 cases was tabulated with self-explanatory details. Some family cases were detailed.

Family 1 was incarcerated in the Budapest ghetto and exposed to significant nutritional deprivation. The family consisted of the mother who was in the third trimester of her third pregnancy and two children aged 4 years and 2 years. After liberation, although not well fed, they had sufficient sustenance to recover. Following emigration to Australia, the family flourished. The eldest son had a T score of -1.6 (height 178 cm) and the second child had a normal T score (height 160 cm). The third child (in utero during mother's nutritional deprivation) had a normal reproductive life, but had a T score of -2.9 (height 150 cm). A fourth sibling, born after the war, had bone densitometry in the normal range [4].

Family 2 was a Slovakian couple (case 2) [Table 1] forced into hiding for 10 months in a shack in the Carpathian Mountains. They were fed only corn, supplied every 2 weeks by their former employee. Overcoming the harsh physical and climatic conditions, they survived. Cessation of the woman's menstrual cycle was attributed to semi-starvation.

Figure 1. DEXA diagnosis of bone mineral content

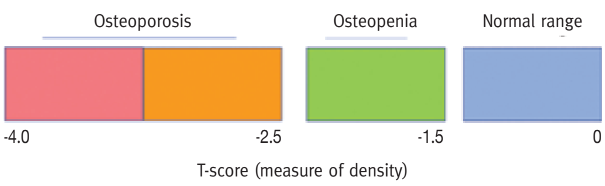

Table 1. Osteoporosis in first generation survivors

Number	Name	Age in camp, years	Incarceration	KZ camp or hiding	Illnesses	Score T / Z
1	Dov	27	Poland, country	Hiding, 3 years	Premature osteoporosis, hip and ribs fractures	-4.4 / -3.1
2	Alisa	21	Slovakia	Hiding in Carpathian Mountains, 10 months	Osteoporosis, fracture pelvis	-4.1 / -2.1
3	Lilach	24	Ravensbruck, Leipzig	8 months	Hip and vertebral fractures	-4.4 / -2.9
4	Safta A	24	Transnistria	2 years	Osteoporosis	-3.4 / -2.8

The nutritional content of corn is reported differently by various sources. It contains only small amounts of fat and protein and is primarily a carbohydrate. Corn contains minerals (magnesium, potassium, and iron) and various vitamins including A, D, and B complex (B1, B3, and B9). Information regarding calcium content varies and some corn grain varieties do not contain this essential mineral.

On liberation, a pregnancy with a stillborn fetus was diagnosed, which required therapeutic abortion. It is possible that after liberation, the mother had been reintroduced to food too rapidly. Later, in Australia, the mother was healthy until age 90, when she suffered pelvic and vertebral fractures and was found to have severe osteoporosis. She recovered from the fractures and lived until 92 years of age. Her post-war reproductive life was normal. Her daughter (case 10) [Table 2] was born and developed under normal nutritional conditions; however, she was also diagnosed with osteoporosis and with moderate risk of fractures [5].

THIRD GENERATION: GRANDCHILDREN OF SURVIVORS

Five cases were tabulated. The family details are described and graphically illustrated. Finding osteoporosis or osteopenia in young people, especially in premenopausal women or relatively young men, is unusual.

Family 3 included a Hungarian-Jewish woman who was incarcerated first in a Hungarian labor camp (Tungsram factory). She was subsequently transferred to Ravensbrueck KZ and then to Leipzig Arbeitslager. She was subjected to hard labor for over 8 months and to severe nutritional deprivation. After the war she returned to Budapest, started a family, and subsequently emigrated to Australia, where she lived to 96 years of age, despite severe osteoporosis (case 3) [Table 1]. During her lifetime she sustained several fractures and was found to have a T score of -4.4. She had three daughters (cases 11, 12, and 13) [Table 2] in good general health, but with low bone density and with T scores of -2.8, -3.3, and -1.5, respectively [Figure 2].

Family 4 was a Romanian family that was deported to Transnistria. The conditions imposed by Romania and the neighboring Ukrainian regimes were extremely harsh. Illnesses resulting from starvation, as well as murder, were common. The grandmother was a prisoner but survived. She immigrated to Israel and subsequently had a normal reproductive life. The women were found to have severe osteoporosis: Safta A (case 4 in Table 1) had a T score of -3.4 and a Z score of -2.86. Her daughter, Sabra A (case 17 in Table 2), had a T score of -2.1 and Z score of -1.9. One of her daughter, Nechda A (case 4 in Table 3), had osteopenia (T score -1.9 and Z score -1.23) and a second daughter, Nechda B (case 5 in Table 3), was diagnosed with osteoporosis (T score -2.6 and Z score -2.1).

Figure 2. Family tree of family 3 **[A]** and family 4 **[B]**
One granddaughter, aged 43 (case 2, in Table 3; the daughter of case 11 in Table 2), while in good health and with regular menstrual cycle, had a low bone densitometry reading with a T score of -2.5

Table 2. Osteoporosis in the second generation (i.e., the children of survivors). All were personally interviewed or were contacted via phone, email, or audio communication

Number	Name	Age in camp, years	Age at diagnosis, years	Medical issue	Score T / Z	Detention
1	Ben	6	64	Metabolic lipid, glucose syndrome	-2.7 / -0.5	6 months in Ghetto Budapest
2	Shmuel	Born, Ghetto Szabadka	59	Metabolic lipid, glucose syndrome, hypertension	-3.0 / -0.1	6 months, metabolic syndrome
3	Moishe	4	64	–	-1.6 / -0.5	12 months in Ghetto Budapest
4	Maalach	In utero	52	–	-2.9 / -1.5	Last trimester in utero, in Ghetto
5	Dvora	2	53	–	-2.3 / -0.8	4 months in Terezin
6	Eli	1	71	–	-2.5 / -1.7	6 months in Ghetto, Budapest
7	VG	–	71	–	-2.2 / -1.0	Born preterm in Prague 1946
8	VL	2	71	Obesity	-1.4 / -1.1	1 month Ghetto Budapest
9	Malka	–	62	–	-1.4 / 0.01	6 months Ghetto Budapest
10	Ruth	–	59	–	-2.2 / -1.3	Born to mother #2 in 1948
11	Miriam	–	70	Obesity	-2.8 / -1.9	Born to mother #3 (Lilach, Table 1) in 1946
12	Agi	–	62	Obesity	-3.3 / -2.3	Born to mother #3 (Lilach, Table 1) in 1947
13	Shosh	–	61	–	-1.5 / -0.2	Born to mother #3, in 1948
14	GF	2 months	69	Spinal stenosis	-2.5 /-2.05	Born in Auschwitz January 1945
15	Hana	3 months	64	Rickets	-2.4 / -0.5	Born in Dachau March 1945
16	Judith	3 months	64	Thyroid	-2.7 / -0.4	Born in Dachau February 1945
17	Sabra	–	69	Obesity	-2.1 / -1.9	Born post-war in Israel

Table 3. Family 3

Number	Name	Gender	Age	T score	Z score
1	Michael	Male	40	-1.7	-0.8
2	Nicky	Female	43	-2.5	-2.1
3	Yvo	Female	56	-1.8	-0.1
4	Nechda A	Female	52	-1.95	-1.23
5	Nechda B	Female	50	-2.6	-2.1

DISCUSSION

Throughout pregnancy fetal skeletal development is constantly evolving; however, the most vulnerable and famine-sensitive time is during the second trimester. The normal development and the pathological effects of various external influences emphasize the minimum requirements for skeletal development [2,3]. Successful skeletal development involves mesenchymal cells turning into osteoblasts and osteoclasts and a daily interaction between bone genesis and lysis. This process requires an adequate supply of minerals (Ca, Ph, Se, and Zn) and vitamins (D, K, and B complex) [2,3]. These nutrients are present in eggs, milk, or meat, which were not available in ghettos, concentration camps, or during hiding.

The effect of starvation or malnutrition in utero was found to lead to premature birth, low birth weight, neonatal morbidity, delayed puberty, reproductive difficulties, metabolic syndrome, increased percentage of malignancies, premature cartilage ossification with paradoxical osteoporosis, arterial wall calcification in adolescents, and premature adult osteoporosis in both genders [4,5,12,15-17].

The definition of metabolic syndrome as described by Eckel and colleagues [16] includes glucose and lipid metabolism, but does not address a parallel bone metabolic disorder. Recognition of changes in bone metabolism was eventually recognized as a late effect of wartime malnutrition in academic papers from Australia [16,17] and Israel [10,16]. The effects were also found during peacetime in England [17-22]. The effect of malnutrition leading to abnormal bone development has been accepted clinically, epidemiologically, and experimentally.

It is unusual to have the opportunity to study metabolic syndrome during a period of starvation/malnutrition, a questionable "privilege" accorded to the Jewish people. The effects of starvation on this unique population was studied in the Warsaw Ghetto by the faculty of a clandestine medical school and published after the war. They described the condition as "Hunger Disease" [11,17].

The incidence of premature osteoporosis in Holocaust survivors has not been sufficiently studied. The possibility of an increased risk of premature osteoporosis in descendants of Holocaust survivors (i.e., possible trans-generational inheritance) has not been investigated. In Israel, a study of osteoporosis was conducted with Holocaust survivors. First, the results were compared to the local population and later to Europeans not exposed to the Holocaust. These studies revealed a higher percentage of osteoporosis post-starvation. Changes were also observed in Australian Holocaust survivors in studies designed to bring attention to some aspects of bone metabolic changes in survivors elsewhere [15,17].

Our research draws attention to the possibility of a three-generational propensity to osteoporosis, While acknowledging osteoporosis as a multi-factorial morbidity, these observations raise the question: Could there be a familial-genetic or an environmental-epigenetic effect in the pathogenesis of osteoporosis? We postulate that nutritional deprivation may result in epigenetic changes and an inheritable predisposition to osteoporosis [23-25]. Sebert in 2011 suggested that, "...the dietary environment interacts with the programmed phenotype to trigger development of metabolic disease" [24].

First, medical practitioners should be aware of possible increased risk of osteoporosis in second and third generation survivors. Early diagnosis would facilitate appropriate treatment including weight-bearing exercise, vitamin D supplementation, and pharmaceutical prescription of appropriate treatments such as bisphosphonates (which may be given in combination with calcium and vitamin D supplements), denosumab, hormone replacement therapy, raloxifene, or teriparatide.

Second, practitioners caring for refugees (e.g., immigrants from Ethiopia and Yemen) or asylum seekers with probable nutritional deficiencies should be aware of the potential effects of starvation during the intra-uterine and neonatal period, and investigate the possibility of any adult metabolic aberrations in lipid, glucose and also in bone minerals, and in both genders.

Third, to be aware that, other than bone mineral metabolism, deficiencies that lead to low nutrition osteopathy (osteomalacia and osteoporosis) may also affect high nutrition osteopathy, deformities, and premature osteoporosis.

LIMITATIONS

This small series of case reports cannot offer any scientific proof on the genesis of osteoporosis. However, as opportunities to study the effects of starvation on humans are limited, it is vital that any data will be recorded.

CONCLUSIONS

Shoah Syndrome is not one generational, the children are also affected. It is of interest that the families with a tendency toward osteoporosis are Holocaust survivors or are from other famine-ravaged countries. It is particularly interesting that their descendants show signs of early osteoporosis, despite adequate nutrition. Further research involving the descendants is clearly needed.

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