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.

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 osteoporosis (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).

---

**Table 1. Osteoporosis in first generation survivors**

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

**Figure 1.** DXA diagnosis of bone mineral content
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].

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.

<table>
<thead>
<tr>
<th>Number</th>
<th>Name</th>
<th>Age at diagnosis, years</th>
<th>Medical issue</th>
<th>Score T / Z</th>
<th>Detention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ben</td>
<td>64</td>
<td>Metabolic lipid, glucose syndrome</td>
<td>-2.7 / -0.5</td>
<td>6 months in Ghetto Budapest</td>
</tr>
<tr>
<td>2</td>
<td>Shmuel Born</td>
<td>59</td>
<td>Metabolic lipid, glucose syndrome, hypertension</td>
<td>-3.0 / -0.1</td>
<td>6 months, metabolic syndrome</td>
</tr>
<tr>
<td>3</td>
<td>Moishe</td>
<td>64</td>
<td>-</td>
<td>-1.8 / -0.5</td>
<td>12 months in Ghetto Budapest</td>
</tr>
<tr>
<td>4</td>
<td>Maalach In utero</td>
<td>52</td>
<td>-</td>
<td>-2.9 / -1.5</td>
<td>Last trimester in utero, in Ghetto</td>
</tr>
<tr>
<td>5</td>
<td>Dvora</td>
<td>53</td>
<td>-</td>
<td>-2.3 / -0.8</td>
<td>4 months in Terezin</td>
</tr>
<tr>
<td>6</td>
<td>Eli</td>
<td>71</td>
<td>-</td>
<td>-2.5 / -1.7</td>
<td>6 months in Ghetto, Budapest</td>
</tr>
<tr>
<td>7</td>
<td>Vg</td>
<td>71</td>
<td>-</td>
<td>-2.2 / -1.0</td>
<td>Born preterm in Prague 1945</td>
</tr>
<tr>
<td>8</td>
<td>VL</td>
<td>71</td>
<td>Obesity</td>
<td>-1.4 / -1.1</td>
<td>1 month Ghetto Budapest</td>
</tr>
<tr>
<td>9</td>
<td>Malka</td>
<td>62</td>
<td>-</td>
<td>-1.4 / 0.01</td>
<td>6 months Ghetto Budapest</td>
</tr>
<tr>
<td>10</td>
<td>Ruth</td>
<td>59</td>
<td>-</td>
<td>-2.2 / -1.3</td>
<td>Born to mother #2 in 1948</td>
</tr>
<tr>
<td>11</td>
<td>Miriam</td>
<td>70</td>
<td>Obesity</td>
<td>-2.8 / -1.9</td>
<td>Born to mother #3 (Lilach, Table 1) in 1946</td>
</tr>
<tr>
<td>12</td>
<td>Agfi</td>
<td>62</td>
<td>Obesity</td>
<td>-3.3 / -2.3</td>
<td>Born to mother #3 (Lilach, Table 1) in 1947</td>
</tr>
<tr>
<td>13</td>
<td>Shosh</td>
<td>61</td>
<td>-</td>
<td>-1.5 / -0.2</td>
<td>Born to mother #3, in 1948</td>
</tr>
<tr>
<td>14</td>
<td>GF</td>
<td>69</td>
<td>Spinal stenosis</td>
<td>-2.5 / 2.05</td>
<td>Born in Auschwitz January 1945</td>
</tr>
<tr>
<td>15</td>
<td>Hana</td>
<td>64</td>
<td>Rickets</td>
<td>-2.4 / -0.5</td>
<td>Born in Dachau March 1945</td>
</tr>
<tr>
<td>16</td>
<td>Judith</td>
<td>64</td>
<td>Thyroid</td>
<td>-2.7 / -0.4</td>
<td>Born in Dachau February 1945</td>
</tr>
<tr>
<td>17</td>
<td>Sabra</td>
<td>69</td>
<td>Obesity</td>
<td>-2.1 / -1.9</td>
<td>Born post-war in Israel</td>
</tr>
</tbody>
</table>

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 ofosteopo-
osteooporosis 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-utero 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 is 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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