Osteoporosis, a very prevalent, potentially debilitating disease, is characterized by decreased bone mineral density (BMD). Decreased BMD has recently been reported in patients suffering from several mental disorders, including schizophrenia and major depression. In these patients the accelerated decrease in BMD can be attributed to drug-induced decreases in levels of estrogen and testosterone, to polydipsia and decreased calcium, to smoking and alcoholism, and to increased activity of several interleukins as well as to hyperprolactinemia and hypercortisolemia. Several of these processes may be prevented or altered in order to prevent or delay decreased BMD.

Decreased BMD in Psychiatric Patients

Rigotti et al. (1986) reported a case of osteoporosis and bone fractures in a man with anorexia nervosa. This report was followed by similar findings in women with the same disorder (Billier et al. 1989; Newman and Halmi 1989; Salisbury and Mitchell 1991). Decreased BMD has been reported in patients with chronic alcoholism (Lindholm et al. 1991) as well as in association with tobacco smoking.

Osteoporosis (decreased BMD) and fractures were reported in 10 male schizophrenia patients with polydipsia (Delva et al. 1989). We (Rojansky et al. 1990; Halbreich et al. 1995) reported decreased BMD in patients with schizophrenia and major depression disorder (MDD) who were treated with neuroleptics or antidepressants. The decrease in BMD was more marked in males,
eight of whom had lumbar compression fractures (as suggested by dual photon absorptiometry), which had not been previously diagnosed (Halbreich et al. 1995). Another group (Schweiger et al. 1993) reported decreased BMD in men and women with MDD. Iliac crest bone biopsies performed on chronic psychiatric patients treated with neuroleptic medications (Kutsuva 1993) revealed evidence of altered calcification and histomorphometry. Thys-Jacobs et al. (1993) reported decreased BMD in women with dysphoric premenstrual syndrome, an intriguing finding that was not confirmed by our group.

The limited number of publications found for this review might suggest that the possibility of osteoporosis is largely underdiagnosed in psychiatric patients. As will be discussed later, it is plausible that osteoporosis might be quite prevalent in patients with major mental disorders, especially if they are treated with psychotropic medications. A preliminary substantiation of this claim is provided by Abraham et al. (1995), who conducted a retrospective survey of elderly chronic patients in a State hospital and found that 25 percent of them had at least one nontraumatic osteoporotic fracture. More extensive epidemiological surveys have not yet been performed. We predict that such surveys would provide an inaccurate picture, especially if they were performed with retrospective chart reviews, because osteoporosis might have been severely underdiagnosed, as is suggested by our observation of the eight men with possible compression fractures who were not clinically diagnosed and were not sent to bone densitometry despite possible complaints of low-back pain.

The Biology and Pathobiology of Bone Dynamics

Osteoporosis can be viewed as a disease of impaired homeostatic regulation (Riggs 1981). As has been eloquently described by Steele (1995), bone is a living, vital tissue that is constantly undergoing change and remodeling. As such, it is also vulnerable to multiple influences on the various processes involved in its dynamics.

Steele (1995) describes the remodeling process: "Bone is constantly being broken down and rebuilt in a process called remodeling. The cellular link between bone-restoring cells, or osteoclasts, and bone-forming cells, or osteoblasts is known as coupling" (p. 87). Steele (1995) also describes what leads to osteoporosis: "Too much bone resorption at the expense of formation results in osteoporosis—a loss of bone strength and integrity resulting in brittleness" (p. 87). The activity of osteoblasts is directly coupled to the activity of osteoclasts, forming a "coupling" theory (Hattner et al. 1965). Disrupted coupling underlies most, if not all, skeletal diseases. The emphasis here will be on bone processes that might be altered in patients with major mental disorders, especially schizophrenia.

Parathyroid hormone (PTH) has been shown to inhibit new bone formation and to stimulate the bone resorption activity of osteoclasts. It is part of the calcium regulatory homeostatic system that also includes the thyroid hormone calcitonin, which inhibits osteoclastic bone resorption. Another facet of the calcium homeostatic system is the sterone vitamin D and especially its metabolite 1,25-dihydroxycholecalciferol (1,25-D), which is a product of metabolism by the liver and the kidney. Not only does 1,25-D affect bone resorption, but it also affects calcium absorption. Its levels are influenced by diet as well as by level of exposure to sunshine. Its decrease might lead to secondary hyperparathyroidism. Synthesis of 1,25-D as well as absorption of calcium in the intestines decreases in states of hypoestrogenism (Hahn 1980).

In this context it is also worth noting that thyroid hormones cause bone absorption directly by stimulating osteoclastic activity (as well as increased secondary activation of the osteoblasts, due to the coupling effect). Hyperthyroidism, excessive thyroid replacement, or thyroid augmentation can be accompanied by osteopenia (Fallon et al. 1983).

A major bone regulatory factor for treated schizophrenia patients is estrogen. Impaired secretion of estrogen might lead to osteoporosis in women of reproductive age. It is well established that osteoporosis can be largely delayed in postmenopausal women by estrogen replacement therapy (Lindsay et al. 1976). Estrogen receptors exist on osteoblast cells, and estrogen can increase gene expression in osteoblasts and increase levels of osteoblast-produced protein as Type I collagen (which is the predominant collagen type in new bone matrix). Estrogen also inhibits osteoclastic bone resorption (Steele 1995). This results in a major net effect of bone formation and a decrease in resorption. Indeed, any process that might lead to hypoestrogenism might increase a person's vulnerability to and probability of osteoporosis.

Although hypoestrogenism is well known as a contributory factor to
ostopenia, hypogonadism has been shown to be a major risk factor for osteoporosis in men as well (Seman et al. 1983; Cummings et al. 1985; Forresta et al. 1985, 1987; Francis et al. 1986; Rigotti et al. 1986; Stanley et al. 1991). Testosterone deficiency has been shown to be associated with profound osteopenia and with a substantially increased risk of fractures. Some other androgens might be involved in this process, but osteoporosis is less studied in men than it is in women.

Several lines of evidence indicate that cytokines are involved in regulation of bone dynamics (Mundy 1993). In the early 1970s it was demonstrated that peripheral leukocytes contain factors that stimulate osteoclast activity. The osteoclast itself originates from mononuclear phagocyte precursor cells. An extensive body of literature documents the indirect regulation of the activity of bone cells, especially the osteoclast. Interleukin 1 (IL-1) stimulates bone resorption both in vitro and in vivo (Gown et al. 1986; Konig et al. 1988), as is the case with tumor necrosis factor α (TNFα), which is produced by both T lymphocytes and macrophages (Bertolini et al. 1986; Konig et al. 1988) and by the T lymphocyte cytokine interferon gamma (IFN-γ) (Vignery et al. 1990). A cytokine that plays an important role in bone-immune system interaction is IL-2, which is produced by T lymphocytes. Its importance might lie in the fact that it initiates a series of cellular events by inducing the proliferation and differentiation of multiple T cell subsets, as well as the production of other cytokines. Human monocytes respond to IL-2 with the induction of IL-1, TNFα, and IL-6 (Musso et al. 1992), potent stimulators of recruitment and formation of osteoclasts.

As is summarized by Steele (1995), osteoblasts are under the control of at least 15 different factors—cytokines, hormones, and growth factors. Among others, they are affected by insulin-like growth factors I (IGF-I) and IGF-II; transforming growth factor β (TGF-β) 1, 2, and 3; platelet-derived growth factor (PDGF); estrogen; testosterone; PTH, vitamin D and its metabolites; acidic and basic fibroblast growth factor (αFGF and βFGF); prostaglandins; and at least several bone morphogenetic proteins (BMPs).

Osteoclasts are also stimulated or inhibited by most of these factors, to which we should add IL-1, TNFα and β, IFN-γ, IL-6, calcitonin, vitamin A, monocyte-macrophage-stimulating factor (M-CSF), and others (Steele 1995).

It is apparent that bone remodeling—absorption and rebuilding—is a dynamic, multidimensional, interactive homeostatic process that can be affected by multiple interventions and pathologies, many of which might be associated with schizophrenia and other mental disorders or with their treatment.

Bone dynamics and the factors that might influence them are summarized in figure 1.

Figure 1. Bone dynamics and processes that might influence them

Adapted with permission, ©1995, Terese Winslow for the Journal of NIH Research (Steele 1995).
Bone Processes That Might Be Impaired in Schizophrenia Patients

Some risk factors for development of decreased BMD and osteoporosis are listed in Table 1. It is apparent that many of these factors might occur in schizophrenia patients, especially those who are treated with neuroleptics (Lacro and Jeste 1994). Comorbidity of alcoholism and drug abuse among schizophrenia patients is quite prevalent, and about 40 percent are heavy smokers (de Leon et al. 1995). One of the first reports on osteoporosis in schizophrenia patients was on patients with polydipsia (Delva et al. 1989), which affects about 25 percent of chronic schizophrenia patients (de Leon et al. 1994). Polydipsia causes a decrease in levels of calcium, which is lost in the urine due to polyuria and decreased renal reabsorption of the mineral.

However, polydipsia and direct calcium imbalance are only one, and probably not necessarily the most important, mechanism of decreased BMD in schizophrenia patients; similarly, immobility is also not a likely cause. It has been demonstrated that in physically healthy, nonmenopausal women, being ambulatory for even relatively short periods (i.e., "routine daily living") is sufficient to retard BMD decrease in weight-bearing bones (Zylstra et al. 1989). Possible dietary deficiency and a relatively decreased exposure to sunshine are probably only minor contributors to decreased BMD in chronic patients (figure 2).

From the onset of interest in osteoporosis in psychiatric patients, focused mainly on women with anorexia nervosa, attention turned to amenorrhea and hypoestrogenism, which are common among these women (e.g., Newman and Halmi 1989). Hypogonadism and amenorrhea are also prevalent among women who are treated with neuroleptics. Since neuroleptic drugs block central dopaminergic action (Baldessarini 1993) and dopamine is a prolactin-inhibiting factor, the use of neuroleptics frequently results in hyperprolactinemia (Siris et al. 1980). The chronic psychotropic-induced hyperprolactinemia may be associated with hypogonadism in both males and females (Levinson and Simpson 1987), which consequently might cause osteoporosis (Klibanski et al. 1981; Schlechter et al. 1983; Greenspan et al. 1986; Ataya et al. 1988; Kartaginer et al. 1990) (figure 3).

Neuroleptic drugs have frequently been reported to adversely affect sexual functioning; there are fewer data on their effects on plasma testosterone. Chronic treatment with antipsychotics (i.e., haloperidol, chlorpromazine, and thioridazine) or some antidepressants might cause

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Table 1. Risk factors for development of osteoporosis

<table>
<thead>
<tr>
<th>Factor</th>
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<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Menopause</td>
</tr>
<tr>
<td>Amenorrhea</td>
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<tr>
<td>Male hypogonadism</td>
</tr>
<tr>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Calcium imbalance (and polydipsia)</td>
</tr>
<tr>
<td>Alcoholism</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td>Various drugs (e.g., lithium)</td>
</tr>
<tr>
<td>Dietary deficiencies</td>
</tr>
<tr>
<td>Lack of sunshine</td>
</tr>
<tr>
<td>Immobility</td>
</tr>
</tbody>
</table>

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Figure 2. Merits of proper diet and sunlight to bone mineral density of chronic patients
Figure 3. Possible mechanisms for neuroleptic-induced decreased bone mineral density

**NEUROLEPTICS**

\[ \downarrow \text{DA} \]

**PROLACTIN**

\[ \downarrow \text{GONADOTROPINS} \]

\[ \downarrow \text{TESTOSTERONE AMENORRHEA & ESTROGEN} \]

\[ \downarrow 1(\text{HYDROXYLATE (IN KIDNEY)}) \]

\[ \downarrow 1.25 \text{ DIHYDROXY VITAMIN-D SYNTHESIS} \]

\[ \downarrow \text{CALCIN absorption (IN INTESTINE)} \]

\[ \downarrow \text{BMD} \]

DA = dopamine; BMD = bone mineral density.


However, it is unclear whether the observed effects are independent of drug-induced hyperprolactinemia (Laughrn et al. 1978). In women with schizophrenia, hyperprolactinemia-induced galactorrhea and menstrual irregularities are common (Jensvold et al. 1966); with some neurotropics they might occur in up to 50 percent of patients (Sandison et al. 1960). Estrogen, or a decrease in its level, might also influence activity of interleukins. These important immune factors may also play a significant role independent of hypogonadism in some mental disorders (schizophrenia and affective disorders), as well as in bone dynamic homeostasis. Both schizophrenia and MDD have been shown to be associated with increased levels of central and peripheral interleukins. Furthermore, IL-2, administered to nonpsychiatric patients (with cancer) provoked dose-related hallucinations, paranoia, disorientation, and apathy; the effects disappeared on IL-2 discontinuation (Denicoff et al. 1987).

An IL-2 hypothesis of the etiology of schizophrenia has been proposed (Smith 1991), because IL-2 can produce both positive and negative symptoms usually associated with schizophrenia. Increased plasma levels of IL-2 have been reported in schizophrenia patients (Rapaport et al. 1989), and increased cerebrospinal fluid levels of IL–2 were found in neuroleptic-free schizophrenia patients (Seibyl et al. 1993). Several other interleukins (e.g., IL–1) might be involved in affective disorders and probably are also involved in schizophrenia. IL–1, as well as TNF–α, IFN–γ, IL–2, and IL–6, has been shown to stimulate osteoclastic activity and therefore promote a negative bone balance, net bone resorption, and decreased bone density (Bertolini et al. 1986; Gown et al. 1986; Konig et al. 1988). It is still unclear if the changes in interleukin activity in both mental disorders and bone dynamics are dependent, parallel mechanisms or whether there is any causative effect or any other direct or indirect association (figure 4).

**Summary**

The suggested decrease in BMD in untreated as well as medicated schizophrenic patients (as well as patients with other mental disorders) might be attributed to accumulated effects of several disease-related and medication-related processes. These processes include hyperprolactinemia, hypogonadism, and increased interleukin activity, as well as polydipsia and impaired fluid and electrolyte balance (mostly calcium), smoking-related processes, dietary and vitamin deficiencies, and decreased exercise and exposure to sunshine. Many of these processes might be prevented or amended to decrease the prevalence of potentially debilitating osteoporosis. Further studies are indicated to confirm the association between mental disorders and decreased BMD and to elucidate the potential underlying mechanisms.
Figure 4. Cytokines and osteoporosis in schizophrenia patients

\[ \text{IL-1} \]
\[ \text{TNF-\alpha} \]
\[ \text{Bone resorption} \]
\[ \text{Bone formation} \]

\[ \text{IL-2} \]

BMD = bone mineral density.

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