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A Review on insulin and vitamin D in pre menopausal and menopausal women

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Abstract

Premenopause is a relatively new term coned in the last twenty years by the medical community to describe symptoms caused by normal hormonal fluctuation that occur as a woman moves close to her menopause. These symptoms can be broad-ranging and diffuse and differ for every woman, causing a lot of confusion and anxiety. During the premenopause, there is an increase in the proportion of cycles that are anovulatory. However, the mechanisms responsible for premenopausal anovulation remain unclear. The anovulatory cycles occurring during the premenopause appear similar to those occurring in adolescents and may reflects an inability to produce a preovulatory surge of gonadotropins after exposure estrogen, atleast in some women. In premenopausal women, bone loss has been significantly associated with low concentration of androgens; however, in premenopusal and menopausal women, low level of androgens and estrogens have been noted, thus sex steroids are important before menopausal to maintain integrity of the skeleton and also important during peri and post menopausal years. Menopause is the point in time when a woman's menstrual periods stop. Some people call the year leading up to a woman's last period "Menopauses", but that time actually is premenopause. Periods can stop for a while and start again, so a woman is considered to have been though menopause only after a full year without periods. Significantly increase in and after the menopause, due to the subsiding ovarian function, compared to the levels in sexually mature women. These high values remain at about this level until the onset of the senium when they start to drop age follicle stimulating hormone due to an age related involution of the pituitary gland. They then remain more or less steady at a slightly increased level until the end of life. The menopause is accompanied by a transition from a gynoid to an android pattern of body fat distribution and an increase in total body fat without a significant change in total percent body fat. Increases are seen in both truncal and subcutaneous abdominal fat mass, with the greatest change seen in intra-abdominal fat mass. Most women transitioning through menopause, especially those with higher percent body fat will experience hot flashes through a mean of 4 to 5 years. Many also have mood disturbances and muscle aches although the link with the menopausal transition is less clear.

Keywords: Premenopause, anovulatory, android pattern, gonadotropins .

Introduction

Premenopause

Premenopause is a relatively new term coned in the last twenty years by the medical community to describe symptoms caused by normal hormonal fluctuation that occur as a woman moves close to her menopause. These symptoms can be broad-ranging and diffuse and differ for every woman, causing a lot of confusion and anxiety. Symptoms of premenopause are extremely individual, but the most common include irregular and a heavy bleeding, insomnia, night sweats and / or hot flashes, vaginal dryness and abdominal weight gain on the physical front. A woman may go in and out of a premenopausal state for as many as 10-13 years before she arrives at true menopause. This means that it is perfectly normal, infact natural for a woman as young as 10 to begin feeling foreign and seemingly inexplicable changes in her body and emotion (Obeagu and Obeagu, 2016).

Premenopause lasts up until menopause, the point when the ovaries stop releasing eggs. In the last 1 to 2 years of premenopause, this drop in estrogen speeds up. At this stage, many women have menopause symptoms(Obeagu et al.,2016).

Symptoms of Premenopause

During premenopausal period some subtle and some not so-subtle changes in the body occur. Some things that will be experienced includes:

(1) Menstrual Irregularity: As ovulation becomes more unpredictable, the length of time between periods may be longer or shorter, your flow may be high or heavy, and one may skip some periods. If you have a persistent change of seven days or more in the length of your menstrual cycle, you may be in early premenopause. If you have a space of 60 days or more between periods, you are likely in late premenopause.

(2) Decreasing Fertility: An ovulation becomes irregular, you ability to conceive decreases. However, as long one is having periods, pregnancy is still possible. If you wish to avoid pregnancy, use birth control until you have had no period for 12 months.

(3) Changes in Sexual Function: During premenopause, sexual arousal and desire may change. But for most women who had satisfaction sexual intimacy before menopause, this will likely continue through premenopause and beyond.

(4) Changing in Cholesterol Levels: During estrogen levels may lead to unfavorable changes in the blood cholesterol levels, including an increase in low density hypoprotein cholesterol – the bad cholesterol- which contributes to an increased risk of heart disease. at the same time, high-density lipoprotein cholesterol- the good cholesterol- decreases in many woman as they age, which also increases the risk of heart disease.

(5) Loss of Bone: With declining estrogen levels, you start to lose bone more quickly than you replace it, increasing your risk of osteoporosis- a disease that causes fragile bone.

(6) Mood Changes

(7) Hot Flashes

Causes of Premenopause

As one passes through menopausal transition, the body's production of estrogen and progesterone rises and fall. Many of the changes one experience during premenopause are as a result of decrease in estrogen.

Pathophysiology of Premenopause

During the premenopause, there is an increase in the proportion of cycles that are anovulatory. However, the mechanisms responsible for premenopausal anovulation remain unclear. The anovulatory cycles ocuring during the premenopause appear similar to those occurring in adolescents and may reflects an inability to produce a preovulatory surge of gonadotropins after exposure estrogen, atleast in some women (Santoro *et al*., 1996). There may be central changes in the hypothalamic pituitary axis that affect gonadotropin secretion. This has been suggested by the lack of response to an estradiol challenge with a luteinizing hormone surge in permenopausal women with dysfunctional literine

bleeding (Santoro *et al*., 1996). However abnormalities in ovarian steroid or peptide secretion may also play a role.

During premenopause, ovarian function appears to be highly variable. Length of menses and the intermenstrual interval varies and anovulatory cycles become more common. Hormone levels may fluctuate widely during this time, and as estrogen level decrease, some of the inherent protective effects of estrogen borne health and endothelial function may also decrease. Thus, the hormonal changes associated with aging may have both short and long term detrimental effects that must recognized, addressed and ameliorated when possible.

Vitamin D and Insulin in Premenopausal Women

In premenopausal women, bone loss has been significantly associated with low concentration of androgens; however, in premenopusal and menopausal women, low level of androgens and estrogens have been noted, thus sex steroids are important before menopausal to maintain integrity of the skeleton and also important during peri and post menopausal years (Judd *et al.*, 1974).

In premenopausal women, higher free testosterone was related with higher insulin, glucose and HOMA- IR after adjustment for BMI and that estrodial was not correlated with those of glucose metabolism (Sutton *et al.,* 2005).There is a reduced risk of breast cancer in association with Vitamin D intake among premenopausal women, but no reduction in breast can in menopausal women (Cho *et al.*, 2011).

Estrogen protects against insulin resistance and that the influence of testosterone on insulin resistance is weak in the presence of estrogen in premenopausal stage (Golden *et al.,* 2007).

Vitamin D and Insulin in Menopausal Women

Menopausal women with osteoporosis are especially linked to exhibit deficiency of vitamin D (Holick, 2007). Seventy-four prevent of a cohort of new diagnosed premenopausal women with breast cancer are at high risk for the disease were reported as exhibition Vitamin D deficiency. As women undergo the menopausal transition, they can experience increase in insulin resistance and other cardiovascular disease factors that are not fully explained by changes in adiposity a sex hormone (Sower *et al.,* 2003).

Women who had the greatest changes in iron over menopause (lower measure of premenopausal iron and greater increases in iron measures over the menopause) had the strongest associations between changes in iron and changes in insulin resistance (Cho *et al.,* 2011).

Estrogen up regulates both the 1-a-ly droxylase enzyme the convent, 25 (04)D to 1, 25 $(OH)_2D$ and increases levels of vitamin D receptor protein, thus depletion of estrogen may in mask a sub-clinical Vitamin D deficiency which may increase the severity of muscle and joint symptom experienced by women entering menopause.

Menopause

Menopause is the point in time when a woman's menstrual periods stop. Some people call the year leading up to a woman's last period "Menopauses", but that time actually is premenopause. Periods can stop for a while and start again, so a woman is considered to have been though menopause only after a full year without periods. After menopause, a woman no longer can get pregnant. It is common to experience the symptoms such as flasher in the time around menopause.

The average age of menopause is 51, but for some women it happens in their 40s or later in their 50s. Sometimes called "the change of life". Menopause is a normal part of life (Nordqvist, 2015).

Causes of Menopause

The hormones estrogen and progesterone regulates menstruation while progesterone is more involved with preparing the body for pregnancy. When the ovaries starts producing less of these two hormones, the premenopause will start.

Infact, by the time a woman is in her late 30s the ovaries start producing less progesterone and estrogen. By the time she is in her 40s, the post ovulations spike in progesterone becomes less emphasized. A woman's fertility starts to decline a long time before she may notice any menopausal or premenopausal symptoms.

As time passes and the ovaries produce less and less estrogen and progesterone, the ovaries eventually shut down completely and the woman no longer have any more menstrual periods. The vast majority female experience a gradual change in menstrual activity, while some go on normally until they suddenly stop (Judd *et al.*, 1974).

Symptoms of Menopause

Expert says that technically, the menopause confirmed when a woman has had no menstrual period for one year. However the symptoms and signs of menopause generally appear well before that one year is over. They may include:

1. **Irregular Periods:** This is usually the first symptoms menstrual pattern changes. Some women may experience a period every two to three weeks, while others will not have one for months at a time.
2. **Lower Fertility:** During the premenopausal stage a woman's life, her estrogen levels will drop significantly, lowering her chances of becoming pregnant.
3. **Vagina Dryness:** This may be accompanied by itching and / or discomfort. It tends to happen during the premenopause. Some women may experience dyspareunia (pain during sex). The term vagina atrophy refers to an inflammation of the vagina as a result of the thinning and shrinking of the tissue as well as decreased lubrication, caused by a lack of estrogen. Approximately 30% of women experience vagina atrophy symptoms during the early post menopause period, while 47% do so during the late post-menopausal period. There are cases of women who experience vaginal atrophy more than a decade after their final period. The majorities of post menopausal women are uncomfortable talking about vaginal dryness and pain and are reluctant to seek medical help.
4. **Hot Flashes:** A sudden feeling of heat in the upper body. it may start in the face, neck, a chest and then spreads upward or downwards (depending on where it starts). The skin on the face, neck or chest may redden and become patchy, and the woman typically starts to sweet. The heart rate may suddenly increase or it may become irregular a stronger than usual. Hot flashes generally occur during the first year after a woman's final period.
5. **Night Sweat:** If the hot flashes happen in bed they are called night sweats. Most women say their hot flashes do not last more than a few minutes.
6. **Disturbed Sleep:** Sleeping problems are generally caused by night sweats, but not always. Sleep disturbance may be caused by insomnia or anxiety. Difficulty falling asleep and staying asleep increase as women go through menopause.
7. **Urinary Problem:** Women tend to be more susceptible to urinary tract infections, such as cystitis. Having to urinate may also occur more frequently.
8. **Moodiness:** This often goes hand-in-hand with sleep disturbance. Experts say that most mood disturbance is triggered by poor sleep.
9. **Problems Focusing and Learning**: Some women may also have short-term memory problems, as well as finding it hard to concentrate on something for long. Some women may not be able to learn as well shortly before menopause compared to other stages of life.
10. More fat building up in the abdomen
11. Hair loss
12. Loss of breast size

If left untreated, these symptoms will gradually taper off gradually over a period of two to five years. However, symptoms can persist for much longer. In some cases, vaginal dryness, itching and discomfort can become chronic, and eventually get worse if left untreated.

Pathophysiology of menopause

Significantly increase in and after the menopause, due to the subsiding ovarian function, compared to the levels in sexually mature women. These high values remain at about this level until the onset of the senium when they start to drop age

follicle stimulating hormone due to an age related involution of the pituitary gland. They then remain more or less steady at a slightly increased level until the end of life (Obeagu et al.,2016). The hormonal characteristics of the menopause or postmenopause respectively are an increase of luteinizing hormone and follicle stimulating hormone levels accompanied by a decrease of estrogen and progesterone which is partly associated with relative androgen predominance. There are increasingly more anovulatory cycles and menstruation becomes more irregular until it finally ceases together. This relative general failure of ovarian steroid production affects above all the hypothalamo - pituitary axis via the negative feedback mechanism. Hence the onset of the climacterium can be determined comparatively easily by monitory serum and Es at the beginning of the cycle and days 3-6 (FSH > 30MU/ML).

However, there should be at least 203 control measurements at interval of 3 months in order to obtain a reliable diagnosis. The ovaries are among the few glands which cease to function prematurely, that is a comparatively long time before the end of life, when reduce hormone production starts with a decrease in progesterone and progresses through ceasing of estrogen production to finally reach a point when no more androgen is produced, which can continue until an age of sixty or above when its function completely stops. Androgen, in particular androstendione and testosterone, continue to be produced in the hilum and interstitial cells even after the menopause. However, the conversion of androgen into estradiol in the ovary is lost because the aromatase enzyme system is closely connected with and dependent on the granulosa cells (Judd et al., 1974).

During the menopause and post menopause periods the thyroid gland does not show any significant changes and its hormone production that is thyroid disorders on the whole do not occur more frequently in the climacteric than in younger years. The cause for the onset of menopause is an increasing decline of ovarian function due to follicle degeneration. As life progresses there is a continuing reduction of a large number of performed follicle, so that at around the age of 50 years only few primordial ovarian follicles remain which still respond to gonadotropin secretion and are able to math into a follicle. With the onset of the chmacteric the number of primordial ovarian follicles presence in ovary has dropped from 500,000 in puberty to a few thousand. Due to the declining number of ovulations and hence the lack of luteal product in the second half of the cycle, progesterone level drop followed by tempo abnormalities and irregularities in the intensity of bleeding. In addition there is also a decrease in estrogen production (Heidenberger *et al.*, 1991). The steady decrease of organ weight presents an additional limiting factor for ovarian function. The maximal ovarian weight peaks between 25 and 30 years of age after which is slowly but regularly decreases. Hence anatrophic ovary in the serum merely weighs about a third of a fully functional one.

Thus the age when the menopause sets in only presents with significant variation between black and throughout America (Flint et al., 1979) the other hand socio-economic differences are discussed. The climacteric syndrome, which is implied in the collection term of “climacteric problems” through a number of signs and symptoms, represent as such the typical pattern of complaints as a sequence of relative estrogen deficiency, starting in the premenopause which can extend over a variable period of time and even span several years until the psotmenopause is reached. This comprises several hormones related components such as the estrogen deficiency syndrome, problems associated with a relative excess amount of estrogen and lack of progesterone (all these occur at the start of the climacterium) and problems which can result from estrogen / gestagen replacement therapy (Fischl *et al.*, 1999).

Menopause and insulin resistance

The menopause is accompanied by a transition from a gynoid to an android pattern of body fat distribution and an increase in total body fat without a significant change in total percent body fat. Increases are seen in both truncal and subcutaneous abdominal fat mass, with the

greatest change seen in intra-abdominal fat mass. This has been reported to increase by as much as 20% to 44% 1, 2. The accumulation of central abdominal fat in women at this is associated with a decline in circulating adiponectin. Adlponectin, an adipokine produced by fat, increase insulin sensitivity by promoting fat oxidation distally in live and muscle. Low serum adiponectin levels are associated with insulin resistance and the metabolic syndrome such that the decline in adiponectin levels are associated with insulin resistance and the metabolic syndrome such that the decline in adiponectin with intra-abdominal weight gain at menopause is believed to have an important role in the development of insulin resistance after menopause.

Whether these metabolic changes are due to the abrupt decline in oestrogen production of menopause or a direct consequence of agency merits consideration. In rodent, oophorectomy increases food intake and body and fat mass, and these effects are reversed by oestrogen therapy. Mice rendered oestrogen deficient by a targeted mutation in the aromatase gene, which is required for oestrogen biosynthesis are obese and insulin resistant. Similarly, the rare event of a mutation in the aromatase gene, and hence inability to biosynthesize oestrogen, results in insulin resistance, T2DM, acanthosis nigncans, hepatic steatosis, and signs a precocious atherogenesis (Maffei *et al.,* 2004). A key observation has been that treatment of a man with an aromatase gene mutation with oestradioil resulted in an improvement of his acanthosis nigricans and hepatic steatosis, improved glycaemic control and the resolution of carotid plagues.

Consistent with these unique models of menopause oestrogen deficiency, treatment of postmenopausal women with oral oestrogen plus progestin or oestrogen alone is associated with a significant decline in insulin resistance over the first year of therapy. Oestrogen plus progestin therapy has also been associated with a significant reduction in the accumulative incidence of treated diabetes (hazard ratio 0.79,95% CI 0.67-0.93, P = 0.004) (Margolis *et al*., 2004), whereas the effect of estrogen alone verus placebo in the woman's health initiative randomized controlled trail approached statistical significance (Hazard ratio 0.88, 95% cl 0.77-1.01, P=0.072). In a 24 month study we also observed a reduction in central abdominal fat in women treated with oestradiol implants.

An important recent observation is the link between obesity, insulin resistant and breast cancer risk indicating the factors produce by adipose tissue not only influence metabolic pathways involved in insulin but also pathways involved in breast cancer development. The accumulation of intra-abdominal fact after menopause may contribute to the increase in risk of breast cancer, an oestrogen dependent malignancy in the postmenopausal years, when circulating oestradiol levels are low, in a prospective cohort study of non-diabetic women with early stage breast cancer, women in the highest fasting insulin levels had three times the risk of reoccurrence and death compared with women with the lowest insulin levels. Other studies have since indicated that the use of metfamin is associated with decrease breast cancer risk.

Together, the available data provides strong evidence that the decline in oestrogen production by the ovaries at menopause contributes to the increase in intra-abdominal fat and insulin resistant which can be ameliorated with oestrogen therapy. Furthermore, the development of insulin resistance after menopause not only has serious health implications in terms of increase risks of type 2 diabetic mellitus and cardiovascular diseases, but may also contribute to pathogenesis of breast cancer.

Vitamin D

Vitamin D refers to a group of fat-insoluble sec osteroids responsible for enhancing intestinal absorption of calcium, iron, magnesium, phosphate and zinc. In human, most important compounds in this group are vitamin D_3 (also known as cholecalciferol)and vitamin D_2 (ergocalciferol) (Holick, 2006). Cholecalciferol and ergocalciferol can be ingested from the diet and from supplement (Calvo *et al.,* 2008). Very few foods contain vitamin D, synthesis of

vitamin D (specifically cholecalciferol) in the skin is the major natural sources of the vitamin. Dermal synthesis of vitamin D from cholecalcified is dependent on sun exposure.

Vitamin D from diet or dermal synthesis from sunlight is biologically inactive, activation requires enzymatic conversion (hydroxylation in the liver and kidney). Evidence indicates the synthesis of Vitamin D from sun exposure is regulated by a negative feedback loop that prevents toxicity but because of uncertainty about the cancer risk from sunlight, no recommendations are issued by the institute of medicine (US), for the amount of sun exposure required to meet Vitamin D requirements. As vitamin D is synthesized in adequate amounts by most mammals exposed to sunlight, it is not strictly a vitamin, and may be considered a hormone as its synthesis and activity occur in different locations. Vitamin D has a significant role in calcium homeostasis and metabolism. Its discovery was due to effort to find the dietary substance lacking in rickets (the childhood form of oesteomalasis) (Eriksen *et al.*, 2002)

Beyond its use to prevent oesteomalaria or rickets, the evidence for other health effect of vitamin D supplementation in the general population is inconsistent (Pitta, 2010). The best evidence of benefit is for borne health (Bjelakovic, 2014). The effect of Vitamin D supplementation on mortality is not clear, with one meta-analysis finding a decrease in mortality in elderly people (Bolland, *et al.*, 2014), and other concluding no clear justification exists for recommending vitamin D. Because it found mounting evidence for a benefit to bone health, though it had not found good evidence of other benefits.

In the liver, cholecalciferol is converted to calcidoil, which is also known as calcifediol, 25-hydroxychole calciferol. The two specific vitamin D metabolite are measured in serum to determine a person's vitamin D status. Part of the calcitriol is converted by the kidneys to calcitriol, the biologically active form of vitamin D.

Vitamin D Deficiency

A diet deficient in vitamin D in conjunction with inadequate sun exposure causes osteomalasis or (rickets when it occurs in children), which is a softening of the bones. In the developed world, this is a rare disease. However, vitamin D deficiency has become a worldwide issue in the elderly and remains common in children and adults (Grant *et al.*, 2005). Deficiency results in impaired bone mineralization and bone damage which leads to bone-softening diseases.

Rickets

Rickets, a childhood disease, is characterized by impeded growth and soft, weak, deformed long bones that bend and bow under their weight as children start to walk. This condition is characterized by bow legs (Lerch *et al.*, 2007), which can be caused by calcium or phosphorous deficiency, as well as lack of vitamin D; today, it is largely found in low-income counties in Africa, Asia, or the middle East (Gibbs, 1994), and in those with genetic disorders such as pseudo vitamin D deficiency rickets. The role of diet in the development of rickets was determined by Edward Mellanby between 1918-1920 (Fischer *et al.*, 1999).

The dietary risk factors for rickets include abstaining from animal foods, vitamin D remains the main cause of rickets among young infant in most countries, because breast milk is low in vitamin D and social custom and climatic conditions can prevent adequate sun exposure.

Osteomalacia

Osteomalasia is a disease in adults that results from vitamin D deficiency. Characteristics of this disease are softening of the bones, leading to bending of the spine, bowing of the legs, proximal muscle weakness, bone fragility, and increased risk for fractures. Osteomalacia reduces calcium absorption and increases calcium loss from bone, which increases the risk for bone fractures (Straube et al., 2009). Osteomalasia is usually present when 25-hydroxy vitamin d level are less than about long/ml. the effects of osteomalasia are

thought to contribute to chronic musculoskeletal pain (Azmina *et al.,* 2010).

Dietary Source of Vitamin D

Vitamin D is found in few dietary sources. Sunlight is the primary source of vitamin D for majority of people, other than supplements (Calvo *et al*., 2005).

Vitamin D_2 (Ergocalciferol)

Fungus, from USDA nutrient database (per 100g). low values in mushrooms for vitamin below indicates incidental exposure to sunlight with activates synthesis a Vitamin D_2. When fresh mushrooms or dried powdered are purposely exposed to artificial sunlight by use of an industrial ultraviolet lamp, Vitamin D level can be controlled at much higher levels.

Vitamin D2, or ergocalciferol found in fungi, is synthesized from viosterol, which in turn is activated when ultraviolet light stimulates eryosterol.

Vitamin D2 from Uv-irradiated yeast baked into bread or mushrrom is boiavaliable and increases blood level of 25 (OH) D. By visual assessment or using a chromometer, no significant discoloration of irradiated mushrooms, as measured by the degree of "Whiteners" was observed.

Vitamin D_3 (Cholecalciferol)

In some countries, staple foods are critically fortified with vitamin D.

=> Vegan sources
Lichen => cladina arbuscular specimen grown under different natural conditions the content of vitamin D_3 ranges from 0.67 to 2.04ug.
=> Animal sources
=> Fish liver oils, such as cod liver oil
=> Fatty fish species, such as
- Salmon, Cooked
- Mackerel, cooked
- Tuna, canned in oil
- Sardines, canned in oil
=> Cooked egg yolk
=> Beef have cooked

Vitamin D_3 (Clolecalciferol) is produced industrially by exposing 7-dehydrocholesterol to UVB, light, followed by purification. The 7-dehydrocholesterol is a natural substance in fish organs, especially the liver, air in wool grease (lanolin) from sheep. Vitamin D_2 is produced in a similar way using ergosterol from yeast or mushroom as a starting materials.

Vitamin D and Disease

Bone Health

In general, no good evidence supports the commonly held belief that vitamin D supplement can help prevent osteoporosis. Its general use for prevention of this disease in those without vitamin D deficiency is thus likely not needed.

Vitamin D deficiency cause osteomalacia, beyond that low level serum vitamin D have been associated with falls, and low bone mineral density (Buttigliero *et al*., 2011). Taking extra vitamin, however, does not appear to change the risk.

Vitamin D and Cancer

Vitamin D supplement have been widely marketed on the internet and elsewhere for their claimed anticancer properties, but taking vitamin supplements has been found to have no significant effect on cancer risk. Insufficient evidence exists to recommend vitamin D to be prescribed for people with cancer, although some evidence suggests hypovitamin D may be associated with a coarse outcome for some cancers (Spector, 2011), and that higher 25-hydroxyvitamin D levels at the time of diagnosis are associated with better outcomes.

Vitamin D and Cardiovascular Disease

Talking vitamin supplements does not meaningfully reduce the risk of strokes, cerebrovascular disease, cardial infarction, or

ischaemic heart disease. supplementation has no effect on blood pressure (Hart, 2012).

Vitamin D and Cognition and Dementia

A systematic review of clinical studies shows an association between low vitamin D levels, cognitive impairment, and higher risk of developing Alzheizers disease. However, lower vitamin concentrations is also associated with poor nutrition and spending less time outdoors. Therefore alternative explanations for the increase in cognitive impairment exists and have direct casual relationship between vitamin D levels and cognitive could not be established (Hart, 2012).

Mortality

Vitamin D_3 supplementation has been tentatively found to lead to a reduced risk of death in the elderly but the effect has not been deemed pronounced or certain enough to make taking supplements recommendable.

With regards to the risk of death, high blood pressure levels appear to be associated with a lower risk of death, but it is unclear if supplementation can results in this benefit. Both an excess and a deficiency in Vitamin D appear to cause abnormal functioning and premature ageing (Avenell et al., 2009). The relationship between serum calcidiol level and all cause mortality is parabolic. Harm from Vitamin D appears to occur at a lower Vitamin D level in the black population then in the white population (Bjelakovic *et al*., 2014).

Vitamin D and Menopause

It is increasingly recognized that vitamin D deficiency affects more than just bone health, links between Vitamin D deficiency have been established or purported for diabetes, the metabolic syndrome, cardiovascular disease, and cancer.

Most women transitioning through menopause, especially those with higher percent body fat will experience hot flashes through a mean of 4 to 5 years. Many also have mood disturbances and muscle aches although the link with the menopausal transition is less clear. In many, these symptoms are severe enough to negatively impact their quality of life, work performance, and interpersonal relationship. Current treatments for menopause related symptoms, such as menopausal hormone therapy, antidepressants and anticonvulsants, have significant side effects and serious long term adverse consequences and symptoms recur after treatment discontinuation.

Both our preliminary data in early postmenopausal women shows an association between Vitamin D deficiency and menopause-related symptoms including hot flashes. As Vitamin D protect against experimental secrotonin depletion in rats, one proposed mechanism for symptoms alleviation is prevention of secrotonin decline in menopause.

Both Vitamin D deficiency and the menopausal transition are associated with mood disturbance and musculoskeletal aches. Because estrogen increases the activity of the enzyme responsible activating Vitamin D, the fall in estrogen that occurs during the menopausal transition could uncover previously subclinical vitamin deficiency. Indeed, Vitamin D can improved mood and muscle aches in non-menopausal populations, but its effects in menopausal women where the benefits may be magnified, have not been previously studied.

Diagnosis of Vitamin D

Level of 25 (OH) D (D_2 + D_3)
Diagnosis may be suspected based on any of the following:

- A history of inadequate sunlight exposure or dietary intake.
- Symptoms and signs of rickets, osteomalasia, or neonatal tetany.
- Characteristics borne changes seen on x-ray.

X-rays of the radius and ulna plus serum levels of calcium, phosphate, alkaline phosphatase, PTH, and 25 (OHlD are need to differentiate Vitamin D deficiency from other causes of bone demineralization.

Assessment of vitamin status and serologic tests for syphilis can be considered for infants with craniotabes based on the history and physical examination, but most cases of craniotabe, resolve spontaneously. Rickets can be distinguished from chrondrodystrohy because the latter is characterized by a large head, short extremities, thick bones and normal serum calcium, phosphate and alkaline phosphatase levels.

Tetany due to infantile rickets may be clinically in distinguished from seizure due to other causes. Blood tests and clinical history may help distinguish them.

Bone changes, seen on x-rays, precede clinical signs. In rickets, changes are most evident at the lower ends of the radius and ulna. The diaphyseal ends lose their sharp, clear outline. They are cup-shaped and show a spotty or fringy rarefaction. Later, because the ends of the radius and ulna have become non calcified and radiolucent, the distance between them and the metacarpal bones appears increased the bone matrix elsewhere also becomes, more radiolucent. Characteristics deformities results from the bones bending of the cartilage-shaft junction because the shaft is weak. As heading begin, a white line of calcification appears of the epiphysis, becoming denser and thicker as calcification proceeds. Later the bone matrix become calcified and opacified at the subperiosteal level.

In adults, bone demineralization, particularly in the spine, pelvis, and lower extremities, can be seen on x-rays; the fibrous lamellae can also be seen, end incomplete ribbon like areas of demineralization (pseudofractures, loose lines, milkman syndrome) appear in the cortext.

Because levels of serum 25 (OH) D reflect body stores of Vitamin D and correlate with symptoms and signs of Vitamin D deficiency better than level of the Vitamin D metabolite, 25 (OH) D (D_2 + D_3) measurement is generally considered the best way to diagnose deficiency. Target 25 (OH)D level are > 20 + 24ng/ml (about 50 to 60 mmol/L) for maximal borne health; whether higher levels have other benefit remains uncertain, and higher absorption of calcium may increase risk of coronary artery disease.

If the diagnosis is unclear, serum levels of 1, 25 $(OH)_2$ D and urinary calcium concentration can be measured. In severe deficiency, serum 1, 25 (OH) 2D is abnormally low, usually undetectable. Urinary calcium is low in all forms of the deficiency except those associated with acidosis.
In Vitamin D deficiency, serum calcium may be low or because of secondary hyperparathyroidism, may be normal. Serum phosphate usually decreases, and serum alkaline phosphatase usually incrases. Serum PTH may be normal or elevated.
Type I hereditary Vitamin 3 – dependent rickets results in normal serum 25 (OH)D, low serum 1,25 $(OH)_2$D and calcium, and normal or low serum phosphate.

Insulin resistance and insulin

Insulin is a hormone made by the pancreas that allows your body to use sugar from carbohydrate in the food that one eats for energy or to store glucose for future use. Insulin helps to keep the blood glucose level from getting too high (hyperglycemia) or too low (hyperglycemia). The cells in the body need sugar for engage. However, sugar cannot go into most of the cells directly. Insulin is often described as a “key” which unlocks the cell to allow sugar to enter the cell and be used for energy, insulin helps store the sugar in the liver and releases it when the blood sugar level is low, therefore, insulin helps balance out blood sugar levels and keeps them in a normal range. As blood sugar rises, the pancrease secrets more insulin (Fischl, 1999).

Insulin resistance is defined as a subnormal response to both endogenous and exogenous insulin (Fernandez *et al*, 2008). It is characterized by a decreasing sensitivity of the target tissues to the action of insulin, by elevated blood glucose concentration, and by the increased hepatic production of antherogenic lipids (Fonseca, 2007). In addition to being associated with the termination of the reproductive life in women, menopause coincides with an increase in several co-morbidities, which include insulin resistance.

The accumulation of the central abdominal fat in women at this time is associated with a decline in the production of a protein which is called adipnectin.

Adiponectin, which is produced by fat, is important for the metabolism of glucose and fatty acids. In short, it makes the cells in the body, particularly the muscle and liver cells, more sensitive to the action of insulin. Low serum adiponactin levels are associated with a condition which is called insulin resistance and the metabolic syndrome, such that the decline in adiponetin with the intra-abdominal weight gain at menopause is believe an important role in the development of insulin resistance after menopause.

Diagnosis of insulin

Fasting Insulin Levels

A fasting serum insulin level greater than 25milli/l or 174pmol/l are considered insulin resistance. Some levels applied for levels after 3 hours of last meal.

Glucose Tolerance Testing

During a glucose tolerance test, which may be used to diagnose diabetes mellitus, a fasting patient takes a 75 gram oral dose of glucose. Then blood glucose levels are measured over the following two hours. Interpretation is based on WHO guidelines. After two hours a glycaemia less than 7.8mmol/L (140mg/dl) is considered normal, a glyacemia of between 7.8 to 11.0mmol/l (140 to 197mg/dl) is considered as impaired glucose tolerance test, and a gylcaemia of greater than or equal to 11.1mmol/L (200mg/dl) is considered diabetes mellitus. An oral glucose tolerance test may be normal or mildly abnormal in simple insulin resistance. Often, there are raised glucose levels in the early measurements, reflecting the loss of a postprandial peak (after the meal) in insulin production extension of the testing (for several man hour) may reveal a hypoglycemic “dip” that is a result of an overshoot in insulin production after the failure of the physiologic postprandial and response.

The gold standard for investigating and quantifying insulin resistance in the “hyperinsulinemic euglycaemic clamp”, so called because it measures the amount of glucose necessary to compensate for an increase insulin level without causing hypoglycemia (Insulin level without causing hypoglycemia . It is a type of glucose clamp technique. The test rarely is performed in clinical care, but it is used in medical commonly is referred to as diabetes literature as the GINE value (Muniyappa *et al*., 2008).

The procedure takes about two hours. Through a peripheral vein, insulin is infused at 10-20mll per m^2 per minute. In order to compensate for insulin infusion, glucose 20% is infused to maintain blood sugar levels between 5 and 5.5mmol/L. The rate of glucose infusion is determined by checking the blood sugar level every five minute. Low dose insulin infusions are more useful for assessing the response to the liver, whereas high-dose insulin infusion, are useful for assessing peripheral insulin action (Muniyappa *et al*., 2008).

The rate of glucose infusion during the last thirty minutes of the test determines insulin sensitivity. If high levels (7.5mg/min or higher) are required, the patient is insulin sensitive. Very low levels (4.0mg/min or lower) indicate that the body s resistant to insulin action levels between 4.0 and 7.5mg/min are not defining true and suggest “impaired glucose tolerance and sign of insulin resistance (Muniyappa et al., 2008).

Modified Insulin Suppression Test

Another measure of insulin resistance is a modified insulin suppression test developed by Gerald Reaven of Stanford University. The test correlates well with the euglycaemic clamp, with less operator-dependent error. This test has been used to advance the large body of research relating to the metabolic syndrome patient initially receive 25 Mcg of octreotide in 5ml of normal saline over 3 to 5 minutes via intravenous infusion as an initial bolus, and then, are infused

continuously with an intravenous infusion a somatostatin to suppress endogenous insulin and glucose secretion. Next, insulin and 20% glucose is infused at ratios of 32 and 26mg/m^2/min, respectively.

Blood glucose is checked at zero, 30, 60, 90 and 120 minutes, and thereafter, every 10 minutes for the last half-hour of the test. These last four values are averages to determine the steady-state plasma glucose level (SSPG). Subject with an SSPG greater than 150mg/dl are considered to be insulin resistance (Muniyappa et al., 2008).

Conclusion

Premenopause is a relatively new term coned in the last twenty years by the medical community to describe symptoms caused by normal hormonal fluctuation that occur as a woman moves close to her menopause. During the premenopause, there is an increase in the proportion of cycles that are anovulatory. Menopause is the point in time when a woman's menstrual periods stop. Some people call the year leading up to a woman's last period "Menopauses", but that time actually is premenopause. Periods can stop for a while and start again, so a woman is considered to have been though menopause only after a full year without periods. They then remain more or less steady at a slightly increased level until the end of life. The menopause is accompanied by a transition from a gynoid to an android pattern of body fat distribution and an increase in total body fat without a significant change in total percent body fat. Increases are seen in both truncal and subcutaneous abdominal fat mass, with the greatest change seen in intra-abdominal fat mass. Most women transitioning through menopause, especially those with higher percent body fat will experience hot flashes through a mean of 4 to 5 years. Many also have mood disturbances and muscle aches although the link with the menopausal transition is less clear.

References

Avenell A. Gillespie W. J., L. D., O'Connel D. (2009). Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal oesteoporosis: *Cochrane Database system Review,* 2.

Azmina Govindji R. D. (2010). When its sunny, top up your vitamin D". Ihelsmaih.org Retrieved July 1, 2010.

Bjelakovic G., Gluud L. L., Nikolova D. (2014). Whitfield K., Wetterslau J., simonetti R. G. (2014): vitamin D supplementation for prevention of mortality in adults". Cochrane Database System Review (system review) 1.

Buttighero C., Monagheldu C., Petroni P., Saini A., doghotti, Ciccone G., Berruti A. (2011). "Prognositc role of vitamin D status and efficacy of vitamin D supplementation in cancer patients. *The Oncologist*, **16**(9): 1215-27.

Calvo M. S., Whiting S. J., Barton C. N. (2005). "vitamin d intake: a global perspective of current status". *Journal of Nutrition*, **135**(2): 310-316.

Cho G., Shin J., Vi K. (2011). Serum ferritin levels are associated with metabolic syndrome in postmenopausal women but not in perimenopausal women, **18**: 1120-1124.

Erikson F. F., Glerup H. (2002). Vitamin D deficiency and aging: implications for general health and osteoporosis: *Biogerontology*, **3**(1): 73-7.

Ferandez J. M., Pickup J. C. (2008). "Innate immunity, insulin resistance and types 2 diabetes. Trends Endocrinology Metabolism, **19**: 10-16.

Fischer P. R., Rahman a., Cimma J. P., Kyaw-Myint T. O., Kabir A. R., Talukder K., Hassan N., Manaster B. J., Staab D. B, Duxbury J. M., Welch R. M., Meisner C. A., Haque S., Combs G. F. (1999). Nutritional rickets without vitamin D deficiency in Bangladesh. *Journal of Tropical Pediatrics*, **45**(5): 291-3.

Fischl F. (1999). Hormonersatztherapie (HRT) in perimenopause and menopause, **11**: 12-7.

Flint M. P., Garcia M. (1979). Culture and the climacteric *Journal Biosocial Science*, **6:** 197-200.

Fonsenca V. A. (2007). Early identification and treatment of insulin resistance. Impact on subsequent prediabetes and type 2 diabetes. *Clinical Cornerstone*, **8**(7): 7-18.

Gibbs D. (1994). Rickets and the cripple child: an historical perspective. *Journal of the Royal Society of Medicine*, **87**(12): 729-32.

Golden s. H., Dobs A. S., Vaidya D., Szklo M., Gapstur S., Kopp P. (2007). Endogenous sex hormones and glucose tolerance status inpostmenopausal women. *Journal of Clinical Endocrinology Metabolism*, **92**(4): 1289-1295.

Grant W. B., Holick M. F. (2005). Benefits and requirements of vitamin D for optimal health: a review" *Alternative medicine review*, **10**(2): 94-111.

Hart G. (2012). "Vitamin D supplementation, moderate sun exposure, and control of immune disease. *Discovery Medicine*, **13**(73): 397-404.

Holick M. F. (2007). "Vitamin D deficiency". N. England, **357**(3): 266-81.

Judd H. L., Judd G. E., Lucas W. E. (1974). Endocrine function of postmenopausal ovary: concentration of androgens and estrogens in ovarian and peripheral blood. *Journal of Clinical Endocrinology Metabolism*, **34**: 1020-1028.

Leidenberger F. A. (1991). Klinische endokrinologie Fur Frahenarzte. Springer Verlay Berlin, Heilelberg, *New York*, **33**:334-5.

Lerch C., Meissner T. (2007). Interventions for the prevention of nutritional rickets in term born children. Cochrane database of systematic reviews (online), (4).

Margolis K. L., bonds D. E., Rodabongh R. J., Tinker L., Phillips L. S., Allen C. (2004). Effect of ostrogen plus progestin on the incidence of diabetes in post menopausal women: results from the women health initiative. *Hormone Tiral. Diabetologie*, **47**(7):1175-1187.

Nordqvist, C. (2015). "what is menopause? What are the symptoms of menopause. Medical new today.com/articles/155651.php.

Muniyappa R. Lee S., Chen H., Quon M. J. (2008). "Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations and appropriate usage: *Journal of Physiology Endocrinology Metabolism*, **294**(1): 15-26.

Pittas A. G., Harris S. S., Stark P. C., Dawson-Hughes B. (2007). The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. *Diabetes Care*, **30**(4): 980-986.

Santoro N., Mushayandebuu T., Castracane D. (1996). Evidence for diminished Midcycle ovarian androgen production in older reproductive aged women. *Fertilization Sterilization*, 65: 721-732.

Sower M., Derby C., Jannausch M., Torrens J., Psternak R. (2003). Insulin resistance, hemostatic factors and hormones interactions in premenopausal women. Swan. *Journal of Clinical Endocrinology Metabolism*, **88**: 4904-4910.

Spector S. A. (2011). Vitamin D and HIV: Letting the sun shine in". *Topics in antiviral medicine*, **19**(1): 6-10.

Stranbe S., Andrew Moore R., Derry S, McQuay H. J. (2009). "vitamin D and Chronic pain" **141**(1-2): 10-3.

Sulton-Tyrrell K., Wildman R., Matthews K. (2005). Sex-hormones-binding globulin and the free androgen index are related to cardiovascular risk factors in multiethnic premenopausal women enrolled in the study of women across the nation, **111**: 1242-1249.

Obeagu, E.I., Obarezi, H.C., Obeagu, G.U., Onyenweaku, F., Okafor, C.N., Essein, U.C.(2016). Evaluation of Variations of Haematological Profile of Menstruating Women in Umuahia, Nigeria. Scholars Academic Journal of Biosciences (SAJB). 4(12):1113-1116.

Obeagu, E.I., Obarezi, H.C., Ochei, K.C., Okafor, C.N., Iwegbulam, C.P., Obeagu,G.U., Essein,U.C.(2016). Evaluation of Variations of Haematological Profile of Menopausal Women in Umuahia, Nigeria. Scholars Academic Journal of Biosciences (SAJB). 4(12):1109-1112.

Obeagu EI, Obeagu GU..2016). A review on haematological profile in menstruating, premenopausal and menopausal women. International Journal of Advanced Research in Biological Sciences.2016; 3(11): 92-108.

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