DISCUSSION AND CONCLUSION

Menopause, with its signs and symptoms, occurs at a time in a woman’s life when she is often actively engaged in family upbringing and handling a full-time job, during this time she might also have the responsibility of caring for aging parents. Women are often puzzled by the remarkable changes in mood, sleep patterns, memory loss, and body shape that occur, as well as the onset of vasomotor and urogenital symptoms (Monteleone et al. 2018). It is a biological process characterized by cessation of the menstrual cycle in women, occur between 45 to 55 years of age. Medically, menopause is the permanent cessation of menstrual flow for over a period of 12 months, following the decrease in production of hormones estrogen and progesterone by the ovaries. This may be spontaneous (natural menopause) or iatrogenic (secondary menopause) (Toth et al. 2000; Dasgupta et al. 2012; Davis et al. 2015; Atapattu et al. 2015; Ahuja, 2016).

The hormonal variation during the menopausal transition contributes more to the changes in the distribution of the body fat than general obesity, which has been demonstrated by increased abdominal fat deposition (Poehlman et al. 1995). It has been reported that there are 49% increase in abdominal fat and 22% increase in subcutaneous fat in the postmenopausal stage of women (Dasgupta et al. 2012; Netjasov et al. 2013; Davis et al. 2015).

The menopause is defined in four stages: Premenopause, Perimenopause, Menopause, and Postmenopause. The premenopause is a term used when the levels of reproductive hormones are becoming more variable and start declining. The premenopause starts, when the monthly cycle becomes noticeably irregular in timing. The effects of hormones
withdrawal are also present in this stage of woman’s life. Perimenopause means “around the menopause” refers to menopausal transition years, i.e. a time before and after the date of last menstrual cycle. During perimenopause, the estrogen levels decreased which are produced by the ovaries (ovarian dysfunction). There is a marked fluctuation in the estrogen level. The duration of perimenopause may be 8-10 years. This stage is followed by menopause when the ovaries release very little or no estrogen hormone. The period for one year of amenorrhea confirms the menopause. This phase usually begins at 40-50 years of age. The last stage is the postmenopause, describe when women do not experience any menstrual flow for last 12 months. It is the time in woman’s life when her ovaries become inactive and the woman is considered as infertile. There is no possibility of becoming pregnant and lactation due to continuous drops in the woman’s reproductive hormones i.e. estrogen and progesterone. Postmenopausal women are at the high risk of health conditions, such as osteoporosis and heart diseases. The symptoms of the postmenopause are hot flashes, night sweat, elevated heart rate, insomnia, mood changes, vaginal dryness and some urogenital disorders (Davis et al. 2015; Monteleone et al. 2018).

Vit-D deficiency is widely prevalence across the globe in every age groups of the society. It is a fat-soluble vitamin and synthesizes in the skin. Aging affects multiple steps of metabolism of Vit-D, as aging starts, the skin has reduced efficiency to synthesize Vit-D even upon exposure to the sun (Munir and Birge, 2008). With an increasing age, a decrease in the estrogen level will cause the decline in the Vit-D activity (Song and Park, 2013). It is an important regulator of bone and mineral metabolism and during postmenopause condition, the occurrence of osteoporosis may be correlated with the deficiency of Vit-D.
Lerchbaum (2014), describes that the hot flushes are the most commonly perceived and reported symptoms of menopause. The decreased estrogen levels are believed to cause an induction of noradrenergic hyperactivity, which leads to a heat loss response and the sensation of warmth throughout the body followed by sweats (Casper, 1985). Hot flashes is a menopausal decline in the neurotransmitter like serotonin, with known effects on thermoregulation. It is also reported that symptoms of Vit-D deficiency and postmenopausal condition are almost same such as sleep disturbance, emotional well-being, energy/fatigue, as well as individual symptoms (Lerchbaum, 2014; Leblanc et al. 2014). It also plays a crucial role in modulating innate immune responses towards various pathogens (White, 2008). Moreover, recent studies indicate that Vit-D can regulate adaptive immune response in various inflammatory and autoimmune diseases (Tiosano et al. 2013; Olliver et al. 2013) such as multiple sclerosis, Type 1 diabetes and rheumatoid arthritis (Holick, 2004; Young and Walker, 2005; Azizieh et al. 2016). The role of Vit-D is to influence inflammatory and immune response, due to the presence of nuclear Vit-D receptor (VDR) in most immune cells including monocytes, macrophages and activated T and B lymphocytes (Cohen-Lahav et al. 2006; Mousa et al. 2017). Thus, the active Vit-D inhibits proinflammatory cytokines expression.

Vit-D deficiency has an inverse correlation with the metabolic syndrome or with the incidence and severity of its components (Boucher, 2012). National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III criteria for Asian Indians) (Misra et al. 2004) defined metabolic syndrome as a group of disorders characterized by abdominal obesity, atherogenic dyslipidemia, raised blood pressure, impaired fasting glucose or
insulin resistance (Type 2 diabetes mellitus, T2DM), proinflammatory and prothrombotic status of a person/subjects. If any subject, who is having variations among any of the three or more components are considered as patient with MS. It is observed that Vit-D deficiency in postmenopausal women, who fulfills the presence of these components by having T2DM and any two raised components like hypertension, abdominal obesity, BMI, dyslipidemia, they are categorized under MS.

Hence, we planned our study, to know whether the Vit-D deficiency has a direct correlation with MS in menopausal women or not?

The present study has been carried out by taking 500 female subjects, out of which 400 women who were either in premenopausal (n=200) and postmenopausal (n=200) phase of life were considered as cases. Along with this, n=100 subjects are considered as healthy control group. Since the study has been focused in premenopausal and postmenopausal women who had a Vit-D deficiency and whether they are suffering from MS. The analysis of various biochemical parameters has been done in various categories and was statistically analyzed and discussed. Here, we wish to clarify that we have estimated Vit-D in terms of 25(OH) D not as 1, 25 (OH)_{2} D because 25(OH) D is a stored form and has a half-life of 10-15 days while 1, 25 (OH)_{2} D has a short life span of few hours in all target cells.

In our study, the overall changes in the anthropometric parameters in premenopausal women (n=200) seemed to be within the normal range but they are found significantly increased when compared with control group (Table No. 6; Graph No. 6). Similarly, the overall status of all anthropometric parameters in postmenopausal women (n=200) was significantly increased when compared with control healthy women (Table No. 6; Graph
No. 6). This is consistent with the study of Rosano et al. 2006; Judd et al. 2008; Rodriguez-Rodriguez et al. 2009; Tamer et al. 2012; Lehtinen-Jacks et al. 2016; Pinkas et al. 2017; Patel et al. 2017. Women tend to gain weight and accumulate visceral adipose tissue during the transition through menopause (Tchernof et al. 1998; Tchernof et al. 2000; Sites et al. 2002). The estrogen deficiency tends to cause excessive visceral fat accumulation, insulin resistance, and increasing risks of CVD among postmenopausal women (Tchernof et al. 1998; Sites et al. 2002). It has been suggested that estrogen acts on android fat to enhance lipolysis and on gynoid fat to suppress lipolysis, but enhance lipoprotein lipase activity. Thus, estrogen promotes mobilization of android fat and deposition of gynoid fat (Orgaard and Jensen 2008). Estrogen has favorable effects on the lipid profile and insulin sensitivity (Barrett-Connor, 2007; Bell et al. 2007) thus offering a protective effect against metabolic disorders. The best proved metabolic effect of obesity on circulating androgen hormones is a decline of sex hormone binding globulin (SHBG) levels, with increasing BMI in both pre- and postmenopausal women. The mechanism responsible for this is related to insulin concentration which inhibits the synthesis of SHBG (Lukanova et al. 2004; Netjasov et al. 2013). The decrease in estrogen level during the menopause also been associated with the rise in the level of TG and LDL-C (Ushiroyama et al. 1993) that leads to the onset of hypertension. Postmenopausal women had higher tendency to develop hypertension due to the visceral fat accumulation and activation of the renin-angiotensin-aldosterone system (RAAS) (Regitz-Zagrosek et al. 2007).

The decline in the estrogen level in pre- and postmenopausal conditions are also associated with Vit-D deficiency. In our study, we observed that the decline of Vit-D levels starts even
with the normal estrogen level in premenopausal women (Table No. 13; Graph No. 13). While in postmenopausal women, the Vit-D and estrogen level are significantly decreased. These observations are same as quoted by Faulds and Dahlman-Wright, 2011; Gupte et al. 2015. No diabetes was observed in these subjects but the alterations in the lipid profile, decreased calcium levels with increased PTH levels and inflammatory markers like hs-CRP and IL-6 were observed. (Table No. 15; Graph No. 15).

Calcium ion is an essential structural component of skeletal. Skeletal mineralization in the rate of bone turnover is controlled by number of hormones and the concentration of calcium is affected by factors like absorption of calcium from the intestine and excretion of calcium from kidney (Nordin et al. 2004; Qureshi et al. 2010; Bhale and Ansari, 2014; Patwa et al. 2017; Kalia and Deep, 2017). In the present study, the serum calcium levels are significantly reduced in postmenopausal women i.e. 8.52 mg/dL as compared to premenopausal women i.e. 9.09 mg/dL. Decreased ovarian function and bone mass during menopause are accompanied by altered calcium metabolism. Estrogen levels also affect the bone remodeling by stimulating osteoblast, decrease the number of activity of osteoclast and synthesizing cytokines affecting bone resorption. Decreased estrogen levels also result in increased synthesis of cytokines by osteoblast, monocytes, and T cells and thereby stimulate the bone resorption (Patwa et al. 2017). Desai et al (2012), found that the mean value of serum calcium level was lower and IL-6 was significantly higher in postmenopausal than premenopausal women. These findings are same as observed in our study. IL-6 is a central mediator of acute phase response and a primary determinant of hepatic production of CRP thus Vit-D deficiency leads to increase in these inflammatory
markers. Parathyroid hormones and Vit-D are primary regulators of calcium homeostasis. The increase in PTH levels are observed in postmenopausal women in our study that is supported by Haden et al. 2000; Cerda et al. 2011; Kim et al. 2018 (Table No. 15; Graph No. 15). In our study, we further explained by making two groups in both category i.e. premenopausal and postmenopausal women as Vit-D sufficient (serum vitamin D levels above 30 ng/mL) and Vit-D deficient group (serum vitamin D levels below 30 ng/mL) because it is not necessary that all pre- and postmenopausal women had Vit-D deficiency. In premenopausal women (n=200), only 127 women had a deficiency of Vit-D while, 73 women did not show any deficiency, it means sufficient amount of serum Vit-D levels are present in them. Similarly, in postmenopausal women (n=200), 141 women had a Vit-D deficiency and remaining 59 women had normal/sufficient Vit-D levels. In our study, the premenopausal women who had sufficient Vit-D levels (n=73), showed the nonsignificant changes in anthropometric and biochemical parameters (Table No. 8 and 9; Graph No. 8 and 9). Similarly, in postmenopausal women, we found that 59 women had normal/sufficient Vit-D levels and not yet developed any kind of metabolic diseases. The anthropometric and biochemical parameters were all within the normal range as compared to control healthy women (Table No. 10 and 11; Graph No. 10 and 11). Vit-D deficiency in premenopausal women (n=127) showed the alternation in anthropometric and biochemical parameters and inflammatory markers (Table No. 12 and 13; Graph No. 12 and 13). These observations are same as quoted by Rodriguez-Rodriguez et al. 2009; Adami et al. 2009; Tamer et al. 2012; Abiaka et al. 2013; Ramly et al. 2013; Islam et al.
The association of hypovitaminosis with dyslipidemia seems to be dependent on obesity and age. It has been hypothesized that low serum 25(OH) D concentrations increased serum PTH levels which promote calcium influx into the adipocytes. Intracellular calcium enhances lipogenesis in adipocytes which leads to an altered lipid profile (Cipriani et al. 2014). Another potential mechanism could be mediated through increased adiponectin secretion by Vit-D by increasing expression of adiponectin gene. Adiponectin influences lipid metabolism by enhancing fatty acid oxidation and reducing triglyceride and cholesterol content in liver, skeletal, and cardiac muscles (Jorde et al. 2010; Jorde and Grimnes 2011; Ding et al. 2012; Lee and Shao 2012; Challoumas 2014; Chen et al. 2014; Tamer et al. 2017). It has also been found to increase the concentrations of apolipoprotein A-1, which is the main protein component in HDL-C (Jaimungal et al. 2011). Wehmeier and colleagues demonstrated that the expression of apolipoprotein A-1 gene in both hepatocyte (HepG2) and intestinal (CaCo-2) cells is regulated by VDR modulators EB1089 and ZK191784 (Wehmeier et al. 2008; Ramagopalan et al. 2010; Heikkinen et al. 2011). In vitro, Vit-D metabolites can upregulate lipoprotein lipase, (Querfeld et al. 1999) increasing HDL-C and lowering triglyceride. Vit-D has anti-inflammatory effects, and might, speculatively, reduce insulin resistance by reducing low-grade chronic inflammation, (Chagas et al. 2012; Hewison, 2012) thus lowering triglycerides and increasing HDL-C (Auwerx et al. 1992; Glueck et al. 2016). In premenopausal women, Vit-D could be linked with glucose metabolism by affecting insulin release that is secreted by pancreatic β cells and may also act on insulin
action by stimulating expression of insulin receptor and amplifying glucose transport. These effects of Vit-D may be directly mediated by binding of 1, 25 DHCC to its receptor or may be indirectly through elevated PTH levels or alterations in intracellular cytosolic calcium (Reis et al. 2007; Ahlstrom et al. 2009; Zhao et al. 2010; Hjelmesaeth et al. 2009; George et al. 2012; Mezza et al. 2012; Ferreira et al. 2015). Recently, it has been suggested that Vit-D may inhibit various aspects of the inflammatory response. Vit-D decreases not only the proliferation of purified T (helper) h1 cells but also stimulation of lipogenesis and inhibition of lipolysis (Tamer et al. 2017). It also down-regulates the nuclear factor-κB activity, increases IL-10 production, and decreases IL-6, IL-12, leading to a cytokine profile that favors less inflammation (Sultan et al. 2009; Mathieu and Adorini, 2002; Tamer and Mesci, 2013; Muscogiuri et al. 2014). (Table No. 13; Graph No. 13).

In postmenopausal women (n=141) with Vit-D deficiency, when compared with the control group showed the significant changes in anthropometric and biochemical parameters. This is supported by the study of Moschonis et al. 2009 (Table No. 14 and 15; Graph No. 14 and 15). Menopause is associated with the changes in body weight and fat distribution (Lerchbaum, 2014; Pinkas et al. 2017). In postmenopausal women, the weight gain started in the first year of menopause this may be due to estrogen hormone deficiency. The activation of the RAAS linked with an increase in salt sensitivity and a negative effect on the leptin and the relative increase in androgens. The increase in body fat is often coupled with an increase in insulin resistance, increased blood pressure and dyslipidemia. Due to reduced estrogen level and other hormonal changes postmenopausal women are particularly prone to develop a Vit-D deficiency. The prevalence of Vit-D deficiency in
postmenopausal women has been reported to be 30-70% (Moghassemi and Marjani, 2014). The high BMI and increase BP in these postmenopausal women is due to Vit-D deficiency because it is a fat-soluble vitamin which is stored in adipose tissue and sequestered pool of fat, this cause a low circulating level of Vit-D (Wortsman et al. 2000). This is further supported by Holick, 2004; Snijder et al. 2005. Dyslipidemia in menopause period is characterized by increased triglycerides, cholesterol, LDL-C and decrease in HDL-C concentration (Derby et al. 2009). In postmenopausal women, Schnatz et al (2011), reported the association of Vit-D with atherogenic lipid profiles, this is because Vit-D regulates reverse cholesterol transport. Chacko et al (2011), found that the above set pattern of hyperlipidemia in postmenopausal women. Vit-D deficiency in postmenopausal women showed a positive relationship with HDL-C concentration and apolipoprotein A-1 concentration. Apolipoprotein A-1 is involved in reverse transport cholesterol system that clears the tissue cholesterol. Hypovitaminosis may increase the risk of vascular damage due to non-availability of apolipoprotein A-1 (John et al. 2005) and this is also supported by Pannu et al. 2016. Chen and colleagues reported that the hypovitaminosis were shown to be associated with insulin secretion and sensitivity. Therefore, Vit-D deficiency might cause dyslipidemia because of its effects on insulin secretion and sensitivity (Chiu et al. 2004; Giovannucci et al. 2008; Sultan et al. 2009). In postmenopausal women, the age-related decrease in calcium absorption, perhaps maybe due to falling in Vit-D levels, serum estrogen levels and increase PTH levels (Eastell et al. 1991, Khosla et al. 1997). Souberbielle et al (2001) and Vieth et al (2003), showed in elderly women the association of Vit-D deficiency with high PTH levels. The increase in PTH levels in response to low
serum Vit-D levels maintain ionized calcium at near normal levels so effectively as to mark a fall in ionized calcium due to deficiency of Vit-D (Need et al. 2000). Khosla et al (1997) reported that within the first 20 years after menopause, the direct effects of estrogen deficiency are primarily responsible for the increase in bone resorption. The effects of Vit-D on serum lipids could also be via suppression of PTH secretion as PTH has been reported to reduce lipolysis at least in vitro (Zemel et al. 2000). In addition, Vit-D could affect the serum lipids through an increased calcium level which may reduce hepatic triglycerides formation and secretion (Cho et al. 2005; Zittermann et al. 2009).

Currently, the importance of this vitamin is well known extending ever beyond its traditional role in bone metabolism. This vitamin is now recognized as a steroid hormone and is also ingested by a food. Aging is considered a risk factor for this vitamin deficiency due to several reasons, like a decrease in its own endogenous production, due to a reduction in sun exposure, decrease intake of fortified food and reduction in intestinal absorption. This vitamin deficiency increases the risk of developing the chronic diseases. Different epidemiological studies have reported an association between Vit-D and inflammatory markers (Perlsteins et al. 2011; Khoo et al. 2011; Kabadi et al. 2013; De Vita et al. 2014; Kruit et al. 2016). These authors found the significant ability of Vit-D to suppress the production of cytokines and to modulate the expression of Toll-like receptors (TLR-2 and TLR-4). Other molecular studies describe the association between Vit-D and inflammation, this vitamin modulates the nuclear factor-kβ which in turn is responsible for the secretion of inflammatory cytokines. This leads to modulates the lymphocyte homeostasis (T and B cells) and immunoglobulin productions (Correale et al. 2009; Ritterhouse et al. 2014; Laird
et al. 2014). This is further supported by Gannage-Yared et al. 2003; Mousa et al. 2017. Vit-D deficiency and metabolic syndrome are associated with low-grade systemic inflammation. CRP, an acute phase protein which is synthesized in hepatocytes largely in response to IL-6. It is also a potent marker of low-grade systemic inflammation (Sugunakar et al. 2014). Moreover, hs-CRP is also associated with insulin resistance, hypertension, obesity, MS and its separate components (Haddad, 2012; Vidhyasagar et al. 2013; Siegel et al. 2014; Patel et al. 2015). One possible mechanism is that adipose tissue itself is a source of CRP formation and also a major producer of IL-6, which is a key stimulator of CRP secretion. In obesity, adipose tissue contains an increased number of resident macrophages and T cells, which interact closely with adipocytes to modulate the inflammatory response (Maria et al. 2010) and released high amount of TNF-α and IL-6 into the circulation, which stimulate the production of CRP by the liver and induces insulin resistance (Pickup et al. 1997). We found in our study that the serum level of both inflammatory markers, IL-6 and hs-CRP in postmenopausal women were raised (p<0.001) as compared to the control healthy women (Table No. 15; Graph No. 15). The estrogen deficiency after menopause may enhance IL-6 production by peripheral blood mononuclear cells of postmenopausal women. This may be due to advancing age or changes of the immune system attributed to estrogen deficiency (Kamada et al. 2001; Ranchon et al. 2002; Cioffi et al. 2002; Yasui et al. 2007; Gameiro et al. 2010).

The study is being continued in pre- and postmenopausal women with sufficient and deficient Vit-D status to know the presence of metabolic syndrome. Metabolic syndrome is defined as a cluster of hyperglycemia or insulin resistance, abdominal obesity,
hypertension, and dyslipidemia. Diagnosis of MS is important for reasons—first, it identifies the patients who are at high risk of CVD and T2DM. Second, by considering the relationships between the components of MS, we may be able to better understand the pathophysiology that links them with each other and with the increased risk of CVD. Third, it facilitates the epidemiological and clinical studies of pharmacological, lifestyle and preventive treatment approaches (Huang, 2009). Currently, National Cholesterol Education Program Adult Treatment Panel-III defines MS on the basis of increased and decreased of the following components:

1. Abdominal obesity: ≥90 cm in men and ≥80 cm in women
2. Hypertriglyceridemia: ≥150 mg/dL
3. Low HDL-C: <40 mg/dL in men and <50 mg/dL in women
4. High blood pressure: ≥130/85 mmHg
5. High fasting blood sugar: ≥100 mg/dL

Any patient or subject possesses variations in three or more components are categorized as suffering from metabolic syndrome. Previously, it was also known as Syndrome “X” but now it is known as metabolic syndrome and abbreviated as MS or MetS. The pathogenesis of MS describes that it is state of low-grade inflammation as a consequence of the complex interplay between genetic and environmental factors. Insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state and chronic stress are the factors which constitute the syndrome.
On the basis of the changes in criteria of components of MS, both sufficient and deficient Vit-D groups were analyzed in pre- and postmenopausal women. We observed that sufficient Vit-D in premenopausal women group (n=73), out of total (n=200) premenopausal women and in postmenopausal women (n=59) out of total 200 women had sufficient/normal Vit-D levels along with normal range of the components of MS with nonsignificant changes (p>0.05) when compared with control healthy women group (Table No. 16 and 17; Graph No. 16 and 17), but in the Vit-D deficient group, we observed that not all pre- and postmenopausal women were suffering from MS. In the Vit-D deficient premenopausal women group, 55 out of 127 women showed variations in either one or two of the components of MS i.e. WC and FBS (showing variations in the majority) (Table No. 18 A). So, according to the definition of MS, these 55 premenopausal women did not fulfill the criteria for having the MS. While remaining 72 premenopausal women showed a significant rise in three or more components of MS i.e. HDL-C, TG, and FBS. These 72 premenopausal women are defined as suffering from MS (Table No. 18A). Further, when the components of MS in these 55 premenopausal women as such compared with control healthy women, we did not show any significant variations (p>0.05) among all the components (Table No. 18; Graph No. 18). While when 72 women were compared with healthy control group, we found significant variations (p<0.001) among all the components of MS (Table No. 19; Graph No. 19).

Similarly, in the Vit-D deficient postmenopausal women group, we observed that again some of the postmenopausal women did not show metabolic syndrome. In this group, 45 out of 141 postmenopausal women did not show MS while 96 women showed the presence
of MS. In these 45 postmenopausal women, we found that in majority two components of MS i.e. HDL-C and WC showed variations (Table No. 20A). Hence, no MS is shown in this group as per the definition of metabolic syndrome. In remaining, 96 postmenopausal women showed a significant rise in the majority of three components of MS i.e. HDL-C, WC, BP. Hence, they are defined as suffering from MS (Table No. 20A). The postmenopausal women (n=45) did not show variations among the metabolic syndrome components when compared with healthy control group. Though slight variation occurs in HDL-C (Table No. 20; Graph No. 20). While remaining 96 postmenopausal women showed significant variations among at least three/ four components of MS i.e. HDL-C, WC, BP, FBS (p<0.001) when compared with healthy control group (Table No. 21; Graph No. 21).

In recent years, we have seen the emergence of growing number of literature linking Vit-D deficiency with MS as a whole or with its components. Abdominal obesity, characteristic of a patient with MS, has also been linked to the presence of low concentration of Vit-D. The possible explanations for the role of obesity as a causal factor of hypovitaminosis include decreased exposure to sunlight, sequestration of Vit-D in adipose tissue due to its lipophilic nature (Wortsman et al. 2000) and decreased hepatic synthesis of 25-hydroxy Vit-D due to the hepatic steatosis or to the inhibitory effects of pro-inflammatory cytokines (Earthman et al. 2012; Cipriani et al. 2014; Minambres et al. 2015). The weight gain occurs because women lose fat-free mass after menopause, tend to exercise less and have a greater increase in fat mass (Lovejoy et al. 2008; Lerchbaum et al. 2014). This rise in obesity and especially the visceral fat accumulation results in an increased risk of MS in
postmenopausal women. Increasing age as well as elevated body fat mass results in hypovitaminosis. Pre- and postmenopausal women are at the high risk of developing Vit-D deficiency because Vit-D synthesis is affected by several factors. Thus physical activity, sun exposure, which is necessary for the synthesis of Vit-D in the skin (Pludowski et al. 2013), decreases during menopause (Lerchbaum et al. 2014). Vit-D, as well as the estrogen, are important for calcium absorption during weight loss (Cifuentes et al. 2004), a sufficient Vit-D intake is highly important in pre- and postmenopausal women to prevent the bone loss and the onset of MS. Elevated BP is statistically significantly related to the Vit-D status in women (Gagnon et al. 2012; Song and Park, 2013). As we know, VDRs are distributed on vascular smooth muscle, endothelium, and cardiomyocytes. 1, 25-DHCC suppresses renin gene expression, regulating the growth and proliferation of vascular smooth muscle cell and cardiomyocytes. Therefore, the absence of VDR activation leads to up-regulation of renin-angiotensin system that results in hypertension in postmenopausal women (Martini and Wood, 2006; Awad et al. 2012; Pludowski et al. 2013; Song and Park, 2013; Chon et al. 2014).

The role of Vit-D in glucose and insulin metabolism has been highlighted for the development of T2DM (Chiu et al. 2004; Deleskog et al. 2012). Vit-D promotes pancreatic β-cell function in numerous ways: Firstly, by direct actions in which activation of Vit-D occurs in pancreatic β-cells by the intracellular 1-α-hydroxylase enzyme. Vit-D enhances insulin secretion and promotes β-cell survival by modulating the generation and effects of cytokines. The anti-apoptotic action of Vit-D is mediated by down-regulating Fas-related pathways (Fas/Fas-L) (Norman, 2006; Eliades and Pittas, 2010). Secondly, by indirect
actions, Insulin secretion is a calcium-dependent process and is influenced by calcium flux through the cell membrane by rapid responses (Norman, 2006). Vit-D regulates calbindin, a cytosolic calcium-binding protein found in β-cells. It acts as a modulator of depolarization-stimulated insulin release via regulation of intracellular calcium. Thus, Vit-D could indirectly affect insulin secretion additionally by regulating calbindin. Another plausible mechanism could be one whereby low Vit-D status induces secondary hyperparathyroidism (SHPT). The raised PTH inhibits insulin synthesis and secretion in β-cells and insulin resistance in target cells by regulating intracellular calcium levels. The SHPT may actually cause a paradoxical increase in intracellular calcium and in turn may impair the calcium signal needed for glucose-induced insulin secretion, this is known as the “calcium paradox” (Fujita and Palmieri, 2000). Though this is not a part of our study but it was observed that in postmenopausal women with deficient vitamin D levels, the fasting blood sugar levels were on the higher side of normal range which indicated that the hypovitaminosis was a positive predictor for the occurrence of T2DM.

Dyslipidemia and proinflammatory and prothrombotic state are also the components of MS. The low-grade inflammatory status also suggested to the onset of MS. The hormonal form of Vit-D can inhibit the production of cytokines, TNFα and IL-6 via VDR, which are expressed in monocytes and activated T lymphocytes (Yin and Agrawal, 2014; Whitcomb et al. 2012). The mechanism between the serum lipids and the VDR levels is basically due to intestinal absorption, lipogenesis, and lipolysis which are decreased in Vit-D deficiency. Hypovitaminosis could contribute an atherogenic lipid profile which is an important risk factor for coronary artery diseases (Wang et al. 2012; Schmitt et al. 2018). A significant
positive correlation between 1, 25-DHCC, and apolipoprotein-A1 with HDL-C level has been reported. Schmitt et al (2018), proposed that the VDR interferes with total cholesterol concentration by regulating at the genetic level and the synthesis of bile acid from the cholesterol.

Further when we compared the status of MS in both pre- and postmenopausal women we found that premenopausal women had normal E2 levels i.e. 76.87±19.9 which are almost same as in control group (76.89±15.21), but Vit-D deficiency was present in them (Table No. 13; Graph No. 13). While, in case of postmenopausal women, the onset of MS is due to estrogen and vitamin D deficiency (Table No. 15; Graph No. 15). As the age advances both hormone act in concert resulting in the onset of MS (Godala et al. 2014). Thus, the severity of MS is more in postmenopausal (48%) as compared to premenopausal women (36%) (Table No. 22; Graph No. 6), also statistically proved by chi-square test (Table No. 23 and 24). Hence, these women are more prone to develop T2DM and CVD. Vit-D deficiency in postmenopausal women with MS had more chances to precipitate osteoporosis also (Kim et al. 2012; Godala et al. 2014).

To prove the deficiency of Vit-D and its association with MS, we did the correlative study by analyzing several correlations among the parameters with a Vit-D deficiency in both pre- and postmenopausal women. In premenopausal women, Vit-D deficiency is inversely associated with all the anthropometric parameters (Table No. 25; Graph No. 25). This is same as quoted by McGill et al. 2008; Majumdar et al. 2011; Abiaka et al. 2013; Muley and Iyer. 2014; Lethinen-Jacks et al. 2016; Toor et al. 2016; Wimalawansa et al. 2018. In our study, we observed that similar pattern is present in postmenopausal women (Table
No. 30; Graph No. 30) and this is consistent with Tworowska-Bardzinska et al. 2008; Lagunova et al. 2009; Durga-Prasad et al. 2012; Joshi et al. 2013; Saneei et al. 2013; Bansal et al. 2014; LeBlanc et al. 2014; Agarwal et al. 2014; Mitra et al. 2016; Schmitt et al. 2018; Rani et al. 2017; Tamer et al. 2017; Schmitt et al. 2018). The association of Vit-D deficiency with BMI and WC is due to deficiency of VDR on the surface of the tissue or organs. Although, Vit-D is a fat-soluble vitamin which is not easily released from adipose tissue once absorbed among the obese individuals (Muley and Iyer, 2014). Vit-D is further correlated with biochemical parameters, we observed that Vit-D deficiency is negatively correlated with FBS, TG, TC, and LDL-C, while positively correlated with HDL-C in both pre- and postmenopausal women (Table No. 26 and 31; Graph No. 26 and 31). This is same as quoted by Lu et al. 2009; Lee et al. 2009; Jorde et al. 2010; Chacko et al. 2011; Durga-Prasad et al. 2012; Song and Park, 2013; Pekkanen et al. 2015; Cypiene et al. 2015; Glueck et al. 2016; Alyami et al. 2016; Rani et al. 2017; Tamer et al. 2017; Schmitt et al. 2018; Patel et al. 2017. Several mechanisms have been identified that explain the effects of Vit-D on lipids and lipoproteins. In vitro, Vit-D metabolites can up-regulate lipoprotein lipase activity (Querfeld et al. 1999), increasing HDL-C and lowering TG (Glueck et al. 2016). In our study, we showed the low HDL-C and increased WC, the most usual factors of metabolic abnormality in postmenopausal women. Altered lipid profile and Vit-D deficiency both can be influenced by anthropometric parameters (BMI and WC) and physical activity, exposure to sunlight and diet (Patel et al. 2017). Pasco et al (2009), reported that the association between Vit-D and parathyroid hormone. The serum PTH concentration has an important role in the mechanism of insulin resistance. Lee et al in
2009, showed that Vit-D levels are negatively correlated with MS and independent of serum parathormone level (Kilic et al. 2012). Hyperparathyroidism is secondary to decrease in Vit-D levels was thought to be the mechanism causing insulin resistance (Kamycheva et al. 2004). George et al (2013), reported that low serum Vit-D levels were related to increased PTH levels which can stimulate the calcium influx into the adipocytes. This finding is consistent with our findings, which indicates the low levels of Vit-D was associated with increased PTH and low calcium levels in postmenopausal women (Khosla et al. 1997; Zemel et al. 2000; Xue et al. 2001; Holick. 2002; Need et al. 2004; Moschonis et al. 2009; Adami et al. 2009; Vuceljic et al. 2012; Tamer et al. 2012; George et al. 2012; Kota et al. 2013; Yikilkan et al. 2013; Shilbli-Rahhal and Paturi, 2014; Capatina et al. 2014; Masoni et al. 2014; Bhaale and Ansari, 2014; Kim et al. 2018; Barrea et al. 2017). While, Nordin et al (2004), contradict our findings by explaining the positive correlation between serum Vit-D and PTH levels. In postmenopausal women, there is severe calcium deficiency and it is mainly due to Vit-D deficiency (Nordin, 2010; Zhang et al. 2012; Yelne and Anjankar, 2017). (Table No. 27 and 32; Graph No. 27 and 32).

Beyond the role of Vit-D in bone metabolism, recently it is proved that Vit-D also plays an important role in inflammation. In our study, Vit-D deficiency is nonsignificantly correlated with inflammatory markers in premenopausal women. This may be due to the normal levels of estrogen in premenopausal women. (Table No. 28; Graph No. 28). But, in postmenopausal women, Vit-D deficiency is negatively correlated with inflammatory markers (IL-6, r= -0.243, p<0.001 and hs-CRP, r= -0.952, p<0.001) (Table No. 33; Graph No. 33). This may be due to the combined effects of both hormones i.e. calcitriol and
Discussion & Conclusion

Estrogen (Lu et al. 2009; Salekzamani et al. 2011; Nakhjavani et al. 2014; Calton et al. 2015; Gonçalves de Carvalho and Ribeiro. 2016). Since IL-6 stimulates osteoclastogenesis which may be correlated with the circulating levels of TG and insulin resistance, this effects probably due to low calcium and Vit-D hormone. Gannage-Yared et al. 2003; Emanuela et al. 2012 reported that Serum IL-6 elucidate the effects of Vit-D on bone and calcium metabolism An inverse correlation was found between Vit-D deficiency and the components of MS in pre- and postmenopausal condition, as we have discussed earlier (Table No. 29 and 34; Graph No. 29 and 34). This is supported by Alissa EM et al (2014), showed an inverse correlation between Vit-D and three components of MS; TG, FBS, and DBP among the elderly population. In our study the postmenopausal women are more susceptible to the onset of the MS is definitely due to the cumulative deficiency of anti-inflammatory hormone i.e. Vitamin D and cardio-protective hormone i.e. estrogen.

CONCLUSION:

The Vit-D endocrine system has provided a new area for investigation of novel approaches for the prevention and treatment of wide range of diseases like MS, CVD, and T2DM. The deficiency of Vit-D is related to the commencement of MS which is nowadays very common in menopausal women of middle and advanced-aged. The deficiency is more prevalent in premenopausal women due to which these women suffer from MS which could be prevented by supplementation of Vit-D but in postmenopausal women due to the deficiency of estrogen hormone along with the fall in vitamin D hormone, the severity of metabolic syndrome is more and could lead to various health complications in them.

“Hence, we can say that Vitamin D is a biomarker of Lifestyle”
**SUGGESTIONS:**

For the prevention of Vitamin D deficiency which is one of the risk factor for the occurrence of metabolic syndrome in the pre- and postmenopausal women are advised to take following measures-

- Exposure of skin to the sunlight with less covered clothing for at least 15-25 min between 10 A.M. to 1 P.M.
- Modification in lifestyle i.e. more exercise, yoga, and outdoor activity.
- Should make changes in the dietary pattern (low carbohydrates and fat) and
- Should take an adequate vitamin D intake either in forms of diet (fatty fish like tuna, mackerel, and salmon, cod liver oil and some fortified products) or in forms of supplementation.

Lastly, time-to-time nutritional public health awareness campaign should be organized by different organizations especially for premenopausal women to let them know about the importance of vitamin D.