CHAPTER 1
INTRODUCTION

DIABETES: THE LARGEST GLOBAL HEALTH EMERGENCY

Diabetes is one of the largest global health emergencies of the 21st century (IDF 2019, 2017, 2015). As per 2019 International Diabetes Federation (IDF) Atlas diabetes is a major health issue that has reached alarming levels: today, nearly half a billion people are living with diabetes worldwide.

The global prevalence of diabetes in **2019** is estimated to be **9.3%** (463 million people) in age group **20–79 years**, and include **both type 1 and type 2 diabetes**, **diagnosed and undiagnosed.** Based on current trends of the IDF 2019, it is estimated that there are currently 463 million people with diabetes worldwide and this number is set to rise to **10.2%** (578 million) by **2030** and **10.9%** (700 million) by the year **2045**. One in two (50.1%) people living with diabetes do not know that they have diabetes. (Fig 1.1).

As shown in Fig 1.1 IDF estimates since 2000 have shown alarming increases, tripling in 2019 estimate of 463 million. Projections for the future have clearly indicated that the global impact of the diabetes likely to continue increasing considerably.

THE INCREASING BURDEN OF DIABETES IN SOUTH EAST ASIA AND INDIA

South East Asia has 8.8% (87.6 million) adults aged 20-79 years in 2019 and by 2030, the region is predicted to grow to about 9.7 % (115 million) and 11.3% (153 million) by 2045. In South East Asia region over 1 million people died due to diabetes in 2019 - the second highest numbers of deaths of all the IDF regions (IDF 2019).

Among all nations China ranked first and India ranks second as regards the prevalence of diabetes in the year 2017 for the age group 20-79 yrs and the diabetes related health

expenditure is very less in the Indian context in comparison to the proportion of number of adults with diabetes (IDF 2017 and IDF 2019) (Fig 1.2). However as far as the estimates of 2045 is projected by IDF 2017, India would rank first and China ranks second as regards the prevalence of diabetes in the age group of 20-79 y. This indicates that India poses an alarming threat to the increasing burden of diabetes in the coming years.

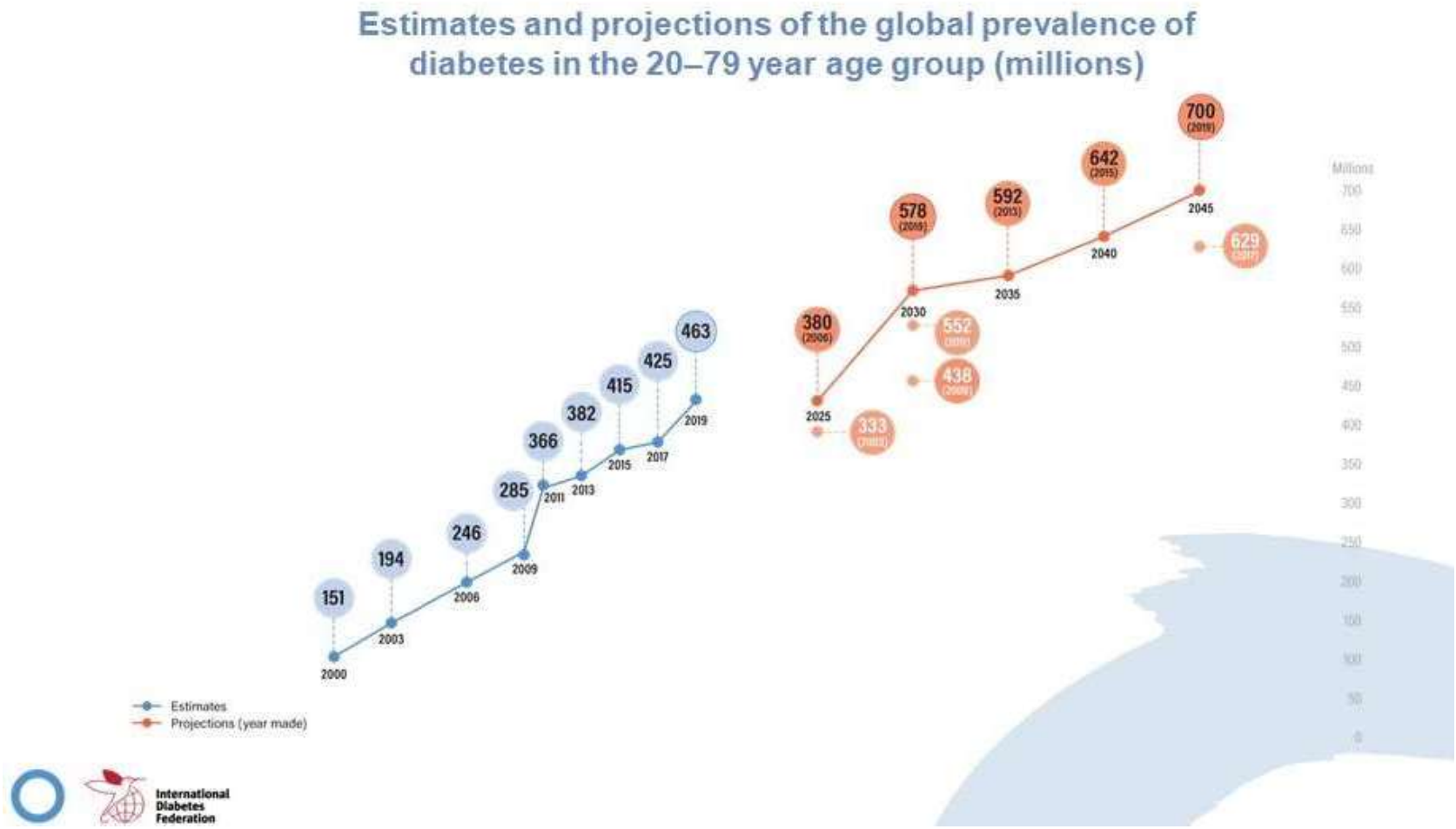
The number of people with diabetes in India started to rise in 1980s and 1990s and from the year 2000 onwards, there has been an explosion of the number of people with diabetes in India. The problem of diabetes has been rising in leaps and bounds in India particularly in type 2 diabetes mellitus (T2DM) (Mohan et al 2015).

The latest NFHS-4 data (2015-2016) stated that the prevalence of diabetes at 7% ranked second amongst all the non-communicable diseases, first being the overweight at 14.6%. At the national level, the 35–49-years (54 years for men) age group, women, and urban areas had a greater prevalence of diabetes than individuals aged 18–34 years, men, and rural areas (Vennu et. al 2019). These results were consistent with previous studies that reported a higher prevalence of diabetes among adults in urban (11.2%) compared with rural (5.2%) India. (Anjana et. al 2017; Anjana et al 2011; Ramachandran et al 2010).

The prevalence rate of diabetes across 28 states and 7 union territories in India has shown that Delhi had the highest prevalence (10,390) of diabetes above the national average (7060) while the lowest prevalence was seen in Rajasthan (2210) (Fig. 1.3) (Vennu et. al 2019). The first Phase of National Family Health Survey (NFHS-5) for the reference year 2019 – 20 has covered 17 states and 5 union territories and the survey for the remaining 14 States/Union Territories of India in the second phase is in progress. Data for Delhi is not yet reported in NFHS-5.

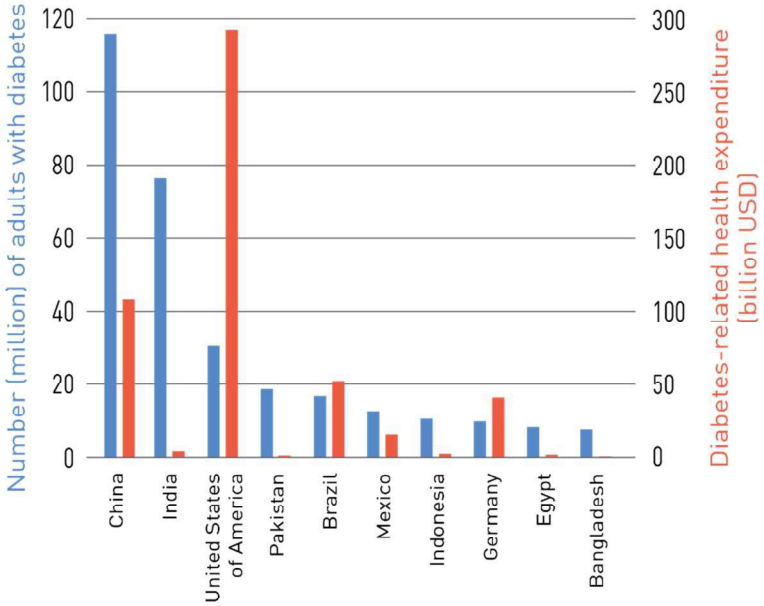
With the above national data, it is recognized that India is struggling with the increasing burden of diabetes since last four decades and IDF 2019 stated that India was the largest contributor to regional diabetes mortality with more than 1 million estimated deaths attributable to diabetes and related complications.

FIG. 1.1: DIABETES AS GLOBAL HEALTH EMERGENCY OF 21ST CENTURY BY IDF 2019



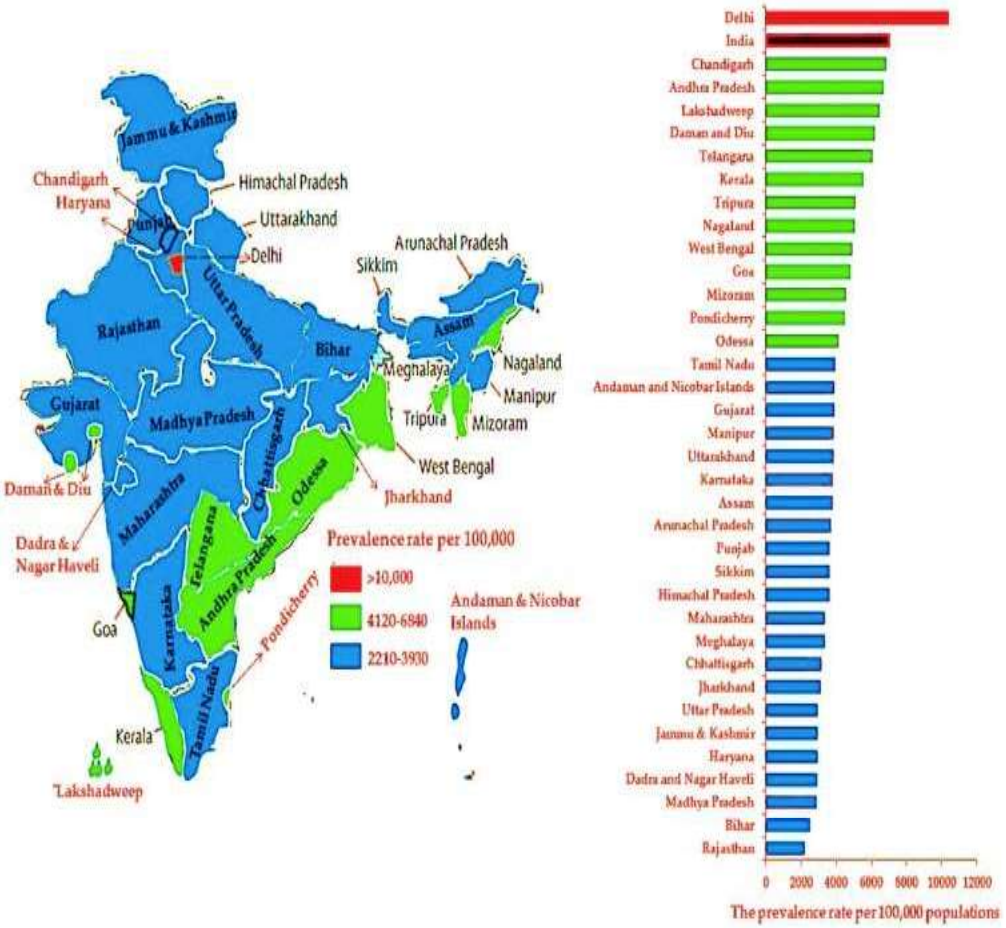
(Adapted from IDF Diabetes Atlas, 9th ed. 2019)

FIG 1.2: NUMBER (MILLION) OF ADULTS WITH DIABETES FOR VARIOUS COUNTRIES WITH THE DIABETES-RELATED HEALTH EXPENDITURE BY IDF 2019



(Adapted from 9th ed. IDF Atlas, 2019)

FIG. 1.3: THE PREVALENCE RATES OF DIABETES AMONG ADULTS AT THE NATIONAL LEVEL AND PER STATE AND UNION TERRITORY



(Adapted from NFHS-4 data, Vennu et. al 2019)

DIABETES RELATED COMPLICATIONS: DIABETES PERIPHERAL NEUROPATHY

Diabetes complications are common among patients with diabetes but, at the same time, are responsible for significant morbidity and mortality (Papatheodorou, 2018). The chronic complications of diabetes are broadly divided into microvascular and macrovascular, with the former having much higher prevalence than the latter (Deshpande et. al, 2008). Microvascular complications include neuropathy, nephropathy, and retinopathy, while macrovascular complications consist of cardiovascular disease, stroke, and peripheral artery disease (PAD). Diabetic foot syndrome has been defined as the presence of foot ulcer associated with neuropathy, PAD, and infection, and it is a major cause of lower limb amputation (Tuttolomondo et al, 2015).

A majority of people with diabetes are unaware of having diabetes complications. However, most complications can be detected in their early stages by screening programmes (ADA 2017). Diabetes dramatically increases the risk for a wide variety of complications which if undetected can have a devastating impact on quality of life and place a substantial burden on health care cost (Girach et al, 2006).

Owing to the detrimental risks posed by the secondary complications it seemed important to study implications of secondary complications. The attention to study macrovascular complication- CVD, has been there since many decades as there has been wealth of research addressing to macrovascular complication. But research to address neuropathy in diabetes has gained attention in past two - three decades. Diagnosis of DPN is crucial as it can lead to substantial discomfort and pain. In more advanced cases it can lead to non healing foot ulcerations, amputations and loss of ambulation deteriorating quality of life.

Previously, American Diabetes Association recommended that people with diabetes should have an annual foot exam to identify high-risk conditions (ADA, 2012). But recently ADA recommends that all patients should be assessed for diabetic peripheral

neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter.

However, the assessment of Diabetes Peripheral Neuropathy(DPN) has been challenging since past few decades (Wang et al, 2017) due to different tools and varying screening instruments used to assess DPN (discussed in review of literature). Recently, Monofilament and vibration perception tests are commonly used screening tools, recommended by several clinical guidelines to detect diabetic peripheral neuropathy (DPN) or even to predict the risk of foot ulcer formation (ADA, 2018 and ADA, 2020).

From some studies across the World it can be said that the prevalence of DPN varied from as low as 8% to as high as 59% (Young et al, 1993, Partanen et al 1995, Deli et al 2013, Dyck et al, 1993) due to different study definition of DPN in each study.

Further there is limited evidence for prevalence of neuropathy in diabetes in Indian context. Only few studies report the prevalence of neuropathy in diabetes to range from 26% to 34.9% (Pradeepa et al, 2008, Paul et. al, 2012, Gill et. al, 2014).

The neuropathy in diabetes present with symptoms similar to those which are present in neuropathy due vitamin B12 deficiency and type 2 diabetics which are on the drug metformin may have vitamin B12 deficiency (ADA, 2020).

Thus studying metformin induced B12 deficiency among type 2 diabetics was crucial.

METFORMIN IN T2DM

According to the ADA 2020 guidelines, metformin and lifestyle modifications are the first line therapies in the treatment of type 2 diabetes mellitus. Metformin, a biguanide, was introduced in the United Kingdom in 1958, in Canada in 1972, and in the United States in 1995 (Bailey, 2017). It is the drug of first choice for the treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function.

As of 2009, metformin is one of the only two oral antidiabetics in the World Health Organization Model List of Essential Medicines (WHO, 2009). Due to this, metformin,

either used as monotherapy or as combination therapy with other oral antidiabetic agents or insulin, has become the most widely used antidiabetic drug. Due to widespread use, much is known about its side effects. The most dreaded side effect of biguanides, lactic acidosis, is never a problem with judicious use of metformin (Tomkin, 1973). Gastrointestinal side effects of metformin can be overcome by initiating metformin therapy at a low dose and slowly increasing the dose, by giving metformin after meals, or by utilizing a slow-release metformin preparation. (Bailey, 2008)

The B12 lowering mechanism of metformin is not yet clear though there has been immense research in this area which is not discussed here as it is not the domain of this study. There is intestinal malabsorption of B12 in T2DM adults which makes them potent to B12 deficiency as evident from several studies since four to five decades as explained in the following text.

METFORMIN INDUCED LOW B12 LEVELS IN TYPE 2 DIABETES MELLITUS

The intestinal vitamin B12 malabsorption in T2DM adults on metformin has been reported in as early as 1969 by Berchtold et al in short term duration of 3 months of metformin administration. These were the observations on the mode of biguanide drug metformin which paved way to the study taken up by Tomkin et al in 1971 where he studied long term effect of metformin on type 2 diabetes patients taking metformin for 2 years. In 2003 it was found that short term metformin treatment of 16 weeks in patients with type 2 diabetes was associated with a decrease in vitamin B12 by Wulffelé et. al, 2003 who carried out the first randomized, placebo-controlled study that reports on the effects of treatment with metformin on serum concentrations of B12.

In one early randomised controlled trial by DeFronzo et al. in 1995 metformin decreased the serum vitamin B12 levels by 22% and 29% compared to placebo and glyburide respectively. This side effect of metformin has been demonstrated again in several ensuing cross sectional studies. (Pflipsen, 2009; Sparre Herman et al, 2004; Nervo et al, 2011),

case reports (Bell, 2010; Kumthekar, 2012) and randomised controlled trials (Kos et. al, 2012; de Jager et. al, 2010).

The risk of developing metformin associated vitamin B12 deficiency is greatly influenced by increasing age, metformin dose and duration of use (de Jager et. al ,2010; Ting et. al, 2006). Decrease in vitamin B12 absorption and levels following metformin use typically starts as early as fourth month (Wulffelé et. al, 2003)

Metformin induced B12 deficiency (< 200pg/ml) has been found to **be 5.8% to 33%** (Pflipsen, 2009; Reinstatler et. al, 2012; Qureshi et. al, 2011) and it is said that this wide range of B12 deficiency is due to varied study definition of B12 deficiency because there are no cut offs to define the deficiency levels.

However, there are only few RCTs addressing this issue across the globe (Wulffele et al 2003, de Jager et al, 2010) and none till date in Indian context.

From **few Indian studies** the prevalence of B12 deficiency (B12<200pg/ml) in T2DM adults on metformin was 27.3% by Kumar, et al 2017, 35.5 % by Raizada et al, 2017 where B12 deficiency was defined as B12 < 150pmol/l and 21.4% by Singh et al, 2013 where B12 deficiency was defined as 150-220 pg/ml. In 2018 the first community-based study from rural south India was conducted by Shailendra et al, 2018 and it is reported the prevalence of vitamin B12 deficiency among those with T2DM in India to be 11.2%.

Since there was sufficient recognition to the fact that low serum B12 levels exist in T2DM adults on metformin thus the study population chosen were T2DM adults on metformin. A need was felt to assess vitamin B12 deficiency in such population and probe this issue with closer angles by planning an intervention to address this issue.

The proposed mechanisms to explain metformin induced vitamin B12 deficiency among patients with T2DM include: alterations in small bowel motility which stimulates bacterial overgrowth and consequential vitamin B12 deficiency, competitive inhibition or inactivation of vitamin B12 absorption, alterations in intrinsic factor (IF) levels and interaction with the cubulin endocytic receptor (Wile & Toth, 2010). Metformin has also

been shown to inhibit the calcium dependent absorption of the vitamin B12-IF complex at the terminal ileum. This inhibitory effect is reversed with calcium supplementation (Bauman et al, 2000).

B12-METFORMIN INTERACTION: NUTRIENT-DRUG INTERACTION

In the study by Bauman et al.,2000 since the results for calcium supplementation were significantly associated with the increase in serum holo TCII, it showed that the transfer of B12-IF complex into holo TCII is independently facilitated by calcium despite the B12 lowering effect of metformin. This concludes that the nutrient calcium is overcoming the inhibitory effect of the drug metformin at the conversion of B12+IF complex, thereby releasing B12-IF complex in the terminal ileum for absorption. Thereby calcium seems to reverse the malabsorbtion of vitamin B12 due to metformin in type 2 diabetic males.

One study by Kocaçiftçi et al (2013) compared the effects of metformin versus metformin and calcium treatments of 1000mg on serum vitamin B12 levels in newly diagnosed T2DM and Impaired Fasting Glucose patients. This study found that vitamin B12 levels decreased less with metformin plus calcium therapy compared to only metformin therapy. It may be suggested that additional calcium supplements may prevent B12 deficiency and associated complications in patients on metformin therapy

VITAMIN B12 DEFICIENCY AND ANEMIA IN T2DM ADULTS ON METFORMIN

It is a well-known fact that B12 deficiency can cause macrocytic anemia owing to the hematopoietic role of B12. Thus type 2 diabetic population having metformin induced low B12 levels is potential to suffer from anemia. Some studies available to relate metformin, anemia and B12 deficiency are discussed further

A mastermind study by Donnelly et al, 2020 indicates the risk of Anemia with Metformin use in T2DM. The mechanism is unknown but a reduction in Hb in the first few years after initiation of metformin might be anticipated. However, the study was limited to the measurement

of serum B12 among metformin users and has no mention of B12 deficiency among T2DM adults on metformin.

Raizada et al, 2017 found that there was no decrease in hemoglobin in the Vitamin B12-deficient patients. On comparing patients with Vitamin B12 deficiency (n=58) (serum B12<150pmol/L) to those with normal vitamin (n=125) (serum B12>150 pmol/L), it was found that mean hemoglobin was not significantly different in the Vitamin B12 deficiency and normal Vitamin B12 groups.

Similar results have been reported by de Groot-Kamphuis et al, 2013 where it was reported that metformin use did not predict the chance on having anaemia2.

However, the study results by Aroda et al, 2016 showed different results where anemia prevalence was higher in metformin group, but did not differ by B12 status.

Another cross sectional study from Oman by Al-Hamdi, 2020 showed that overall, 90 (36.3%) patients were found to be anemic, of which 11 (42.3%) participants were in the vitamin B12-deficient group, 15 (28.3%) were in the borderline-deficient group and 64 (37.9%) were in the normal group; these differences were not statistically significant.

WITH THE ABOVE REVIEWED LITERATURE, THE FOLLOWING GAPS WERE IDENTIFIED:

- Limited evidence for the prevalence of DPN and its associated risk factors in Indian setting.
- Limited evidence for the prevalence of B12 deficiency among type 2 diabetics on metformin.
- There is scanty literature to bridge the link between the two diseased conditions: B12 deficiency and DPN, in T2DM adults on metformin in Indian setting.
- Very few studies are there to intervene in the problem of metformin induced B12 deficiency and relate to the cause and effect relationship of metformin-B12 interaction.

- No RCT from India has been found to address the nutrient dug interaction of B12 and metformin.
- Limited evidence to state the prevalence of anemia among T2DM adults on metformin.
- Relationship between B12 deficiency and anemia among T2DM adults on metformin is not clear.
- Further it was thought that the coexistence of diabetes, B12 deficiency and DPN would deteriorate quality of life in T2DM adults so the need was felt to study quality of life to draw a holistic picture of the wellbeing of T2DM adults on metformin.

Keeping in mind the above gaps, the present study was planned with the following rationale.

RATIONALE FOR THE PRESENT STUDY

The study is preliminary of its kind in that it is an attempt to study implications of nutrient – drug (B12 -metformin) interaction among T2DM adults and address metformin induced B12 deficiency among type 2 diabetics by planning an intervention trial.

The reviewed literature suggests that decrease in vitamin B12 absorption and levels following metformin use typically starts as early as fourth month. So the desired population was chosen to be the one on metformin for a minimum of four months.

Further the symptoms of B12 deficiency may be indistinguishable from that of peripheral neuropathy in diabetes. So it was necessary to study neuropathy in relation to metformin induced low B12 levels in T2DM adults.

Vitamin B12 absorption is inhibited by metformin and it was hypothesized that calcium may reverse this effect if calcium supplementation is administered along with routine B12 supplementation given by physician to treat B12 deficiency.

RATIONALE FOR CALCIUM SUPPLEMENTATION IN T2DM PATIENTS WITH LOW VITAMIN B12 LEVELS

Vitamin B12 absorption in gastrointestinal tract forms a complex with intrinsic factor after following a sequence of reaction starting its digestion from mouth. The vitamin B12–IF complex is highly resistant to proteolytic degradation. The complex attaches at its specific receptors on the mucosa of the terminal ileum, a site where its absorption occurs. This stage of vitamin B12 absorption is calcium mediated. Absorption of ionic calcium is obligatory for the B12-IF complex to attach to ileal cell surface receptors, and metformin competes with calcium for the mucosal cell membrane. This form of vitamin B12 malabsorption was reversible with an oral calcium supplement (Bauman et. al, 2000)

Metformin treated type 2 diabetic patients with low vitamin B12 levels and not on any calcium supplementation (who do not consume adequate milk or milk products on a daily basis) form a potential group to intervene with calcium supplementation along with monitoring for vitamin B12 levels because if it comes out to be effective then calcium supplements can be started as a routine line of therapy in treatment of type 2 diabetes.

RESEARCH PROBLEM

It was recognized that metformin causes low serum B12 levels in T2DM adults. If left undertreated, it may cause neuropathy which may present with symptoms indistinguishable from DPN which would further deteriorate the quality of life. Thus it was hypothesized that calcium supplementation would reverse the inhibitory effect of metformin in T2DM adults thereby improving B12 deficiency, neuropathy and quality of life in T2DM.

Keeping the above research problem in mind and the felt need to address the above identified gaps in research the present study was formulated with the following **broad objectives:**

- To assess the prevalence of DPN among T2DM adults on metformin.
- To assess the quality of life among T2DM adults on metformin.
- To do B12 screening among T2DM adults on metformin so as to assess their B12

status.

- To map the prevalence of anemia among T2DM adults on metformin and study it in relation to B12 deficiency.
- To plan an intervention trial to address the metformin induced B12 deficiency among T2DM adults where calcium supplementation would be studied along with routine practice of giving B12 supplementation to T2DM adults with low serum B12.
- To assess the efficacy of calcium supplementation along with B12 supplementation in comparison to B12 supplementation alone among T2DM adults on metformin in relation to B12 deficiency, DPN and quality of life.