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THE DIABETES EPIDEMIC IN INDIA: SOME LESSONS LEARNT

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How India became the epicenter of the diabetes epidemic

Diabetes, one of the world's largest public health challenges[1] has been expanding its horizons exponentially over the last few decades. Diabetes has also become one of the leading causes of mortality along with cardiovascular disease (CVD), respiratory disease, and cancer[2]. In 2019, WHO reported that an alarming 74% of global deaths were due to non-communicable diseases (NCDs), of which 1.6 million deaths were attributed to diabetes, making it the ninth leading cause of death globally[2].

Even up to a couple of decades ago, diabetes was thought to be a disease mainly of the more affluent countries [3]. Today it is most rampant among the lower- and middle-income countries which account for almost 80% of all diabetes cases in the world[3]. Indeed, Asia is the epicenter of the epidemic[4] and India is currently the second largest country with diabetes, next only to China[1]. Over the last 30 years, studies have reported a steady rise in the prevalence of diabetes, in both urban and rural areas of India[5]. From a prevalence of 2.3% in urban and 1.5% in rural areas in the year 1971 **(Figure 1)** it has increased to over 25% of adults with diabetes in large metropolitan cities like Chennai, Delhi and Hyderabad

According to the International Diabetes Federation, India currently has about 74 million people with diabetes and this number is expected to increase to be about 125 million by 2045[1] **(Figure 2)**. Today, the prevalence of diabetes in urban India is twice that of the prevalence in rural India but rural areas are fast catching up. Alarmingly, in most of the states, the rate of pre-diabetes exceeds the rate of diabetes, a forewarning that the epidemic is far from over.

The Indian Council of Medical Research, India Diabetes (ICMR–INDIAB) study is the largest epidemiological study on diabetes, covering all 29 states and 2 union territories of the country. This study, published in *Lancet Diabetes & Endocrinology*, showed wide variations in the prevalence of diabetes within the country. It also reports that a higher percentage of lower socio-economic populations in urban areas of the more affluent states are affected with diabetes than the upper socio-economic groups[6]. **(Figure 3)**. This is a clear indication of the epidemiological transition that has taken place in India during the last 3-4 decades.

The driving forces of the diabetes epidemic - lessons from various studies

The so called 'South Asian Phenotype' detailed in **Figure 4** contributes to the younger age at onset of T2DM and CVD among Indians. While genetic factors are also important, it is the environmental

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Figure 1 : PREVALENCE OF DIABETES IN INDIA (*1971 - 2015*)

Year	Author	Place	Prevalence (%) Urban	Prevalence (%) Rural
1972	Ahuja et al	Multicentre (ICMR)	2.3	1.5
1984	Murthy et al	Tenali	4.7	
1988	Ramachandran et al	Kudremukh	5.0	
1997	Ramachandran et al	Chennai	11.6	
2000	Ramankutty et al	Kerala	12.4	2.5
2001	Ramachandran et al	National Urban Diabetes Study (NUDS)	12.1	
2001	Mohan et al (CUPS)	Chennai	12.1	
2004	Ramachandran et al	Chennai		6.4
2004	Mohan et al (CURES)	Chennai	14.3	
2006	Menon et al	Ernakulam	19.5	
2008	Ramachandran et al	Chennai	18.6	
2009	Vijayakumar et al	Kerala		14.6
2010	Rao et al	Coastal Karnataka		16.0
2012	Murthy et al	Tenali	18.0	
2015	Deepa et al (CARRS)	Chennai	22.8	
		Delhi	25.2	

Figure 2 : Top 10 countries or territories for number of adults (20-79 years) with diabetes in 2021 and 2045

2021 Rank	Country or territory	Number of people with diabetes (millions)	2045 Rank	Country or territory	Number of people with diabetes (millions)
1	China	140.9	1	China	174.4
2	India	74.2	2	India	124.9
3	Pakistan	33.0	3	Pakistan	62.2
4	United States of America	32.2	4	United States of America	36.3
5	Indonesia	19.5	5	Indonesia	28.6
6	Brazil	15.7	6	Brazil	23.2
7	Mexico	14.1	7	Bangladesh	22.3
8	Bangladesh	13.1	8	Mexico	21.2
9	Japan	11.0	9	Egypt	20.0
10	Egypt	10.9	10	Turkey	13.4

IDF Diabetes Atlas, 10th Edition, International Diabetes Federation, 2021

factors that contribute to over 60% of the risk of type 2 diabetes.

The three main risk factors for type 2 diabetes are: 1) Excess intake of carbohydrates leading to increased glycemic load 2) Decreased physical activity 3) Urbanization **(Figure 5)**

The Chennai Rural Urban Epidemiological Study (CURES) revealed that refined grain intake, was positively associated with the risk of type 2 diabetes (T2DM). Specifically, dietary carbohydrates (predominantly contributed by polished white rice) showed an increased risk for T2DM as did the glycemic index and glycemic load of foods[7]. In contrast, fibre and dairy products were found to be protective against T2DM. Consumption of fruits and vegetables also conferred 48% protection against CVD risk factors including T2DM[8]. However, the impact of the quality and quantity of dietary fats cannot be overlooked. In CURES, we reported that MUFA was negatively associated with the risk of T2DM. Appropriate use of cooking oils, cooking methods and encouraging the inclusion of nuts and oilseeds is thus another effective dietary strategy to reduce risk of T2DM[9].

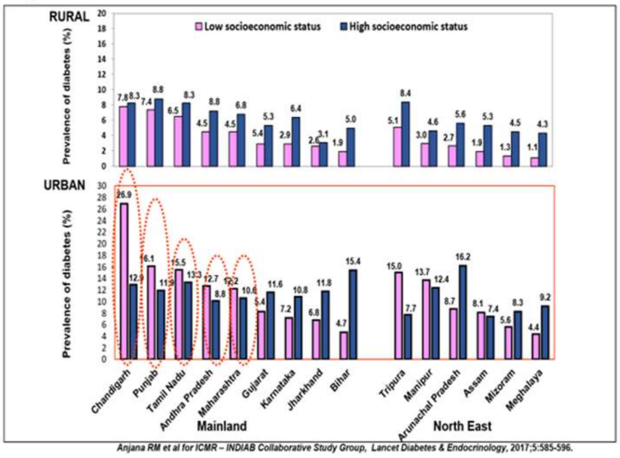
What about nuts?

Our studies showed that consumption of 30g of cashew nuts/day decreased systolic blood pressure and increased HDL (good) cholesterol concentrations in T2DM without adverse effects on body weight, glycemia, or other lipid parameters[10].

We also developed a Food-Based Indian Diet Quality Score (IDQS) for comparing food groups. This showed that diets with the highest IDQS, had the lowest risk of T2DM[11]. Cross sectional studies have their own limitations as it is difficult to establish a cause/effect relationship. In order to study the association of white rice intake with *incident* (i.e., new onset) *diabetes*, we analyzed data from the Prospective Urban Rural Epidemiology (PURE) study. The PURE study was carried out on 132,373 individuals across 21 countries in 5 continents, with the subjects being followed up for 15 years. The study showed a strong association of excess white rice with incident type 2 diabetes, especially in S. Asia where the rice intake is high (**Figure 6)**[12].

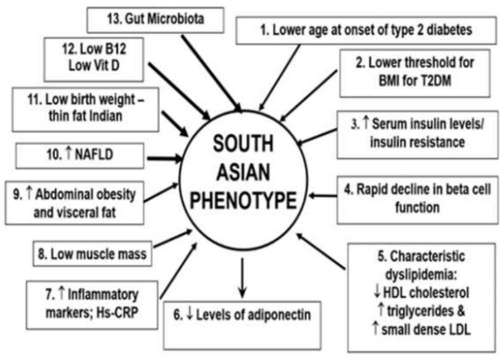
In another study published in the *New England Journal of Medicine* in 2021, we showed for the first time that high glycemic index in the diet is also

Figure 3 : PREVALENCE OF DIABETES STRATIFIED BY SOCIO-ECONOMIC STATUS



Anjana RM et al for ICMR – INDIAB Collaborative Study Group, Lancet Diabetes & Endocrinology, 2017;5:585-596.

Figure 4 : SOUTH ASIAN PHENOTYPE



Mohan V et al, Diabetologia 1986; Ramachandran A et al, Diabetes Res Clin Pract. 2004; Joshi SR, J Assoc Physicians India. 2003; Yajnik CS et al, J Nutr. 2004; Banerji et al, J Clin. Endocrinol. Metab., 1999; Chandalia M et al, J Clin Endocrinol Metab, 1999; Chambers JC et al, Circulation. 2001; Misra A et al, Current Sci, 2003; Abate N et al, J Clin Endocrinol Metab. 2004

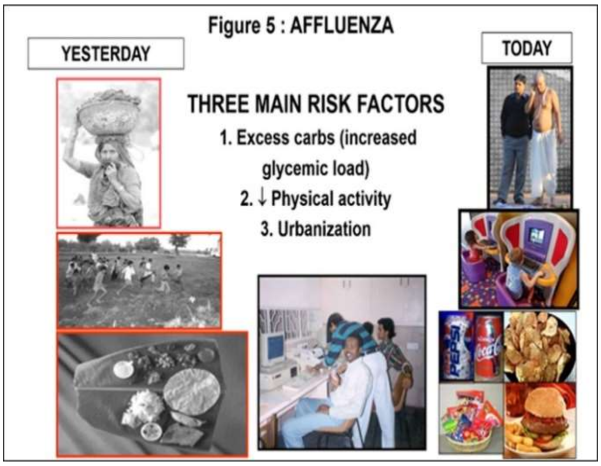
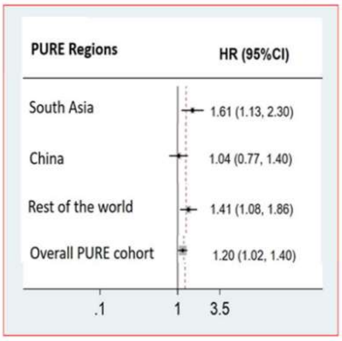


Figure 6 : Hazards ratio (HR) for association of white rice intake with incident diabetes – in different world regions



Bhavadharini B, Mohan V, Dehghan M, Sumathy R, Sumathi S, ... Yusuf S. *Diabetes Care.* 2020;43:2643 - 2650

linked to higher mortality[13]. In another study, we showed that physical inactivity is also another independent risk factor for T2DM **(Figure 7).**

Can T2DM be prevented?

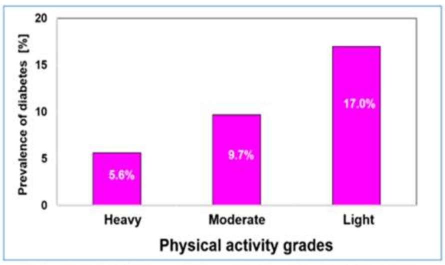
In the ICMR - INDIAB Study, the prevalence of prediabetes ranged from 5.8 to 14.7% in rural areas, and from 7.2 to 16.2% in urban areas. Since the prevalence of prediabetes is substantial, there is a 'golden window of opportunity' to prevent T2DM. There is evidence that Asian Indians progress more rapidly through the prediabetes stage to develop T2DM as compared to people of other ethnic groups. This underscores the need to take up primary prevention of diabetes at the population level. In this context, I would like to share with you the Asiad Colony real life experiment we conducted in Chennai. The Chennai Urban Population Study (CUPS) conducted from 1996 to 1998 showed a significantly higher prevalence of diabetes in the middle-income group (12.4%) compared to the lower income group (6.5%). The results of the study were discussed with the residents of both colonies. After several awareness campaigns, the middle-income colony residents realized the value of physical activity to prevent obesity and diabetes. As they had a vacant plot of land next to their colony, they built a beautiful park adjacent to their colony, by raising funds through their own resources, thereby creating a space to increase their physical activity[14]. A follow-up study was after 10 years showed that, in this middle-income group the prevalence of diabetes increased only marginally from 12.4 to 15.4% (24% increase), whereas in the lower income group where no intervention was done, it increased from 6.5 to 15.3% (135% increase). This study is the first of its kind in India to introduce a "real-world" lifestyle intervention in the prevention of diabetes through community empowerment[15] (**Figure 8)**.

Based on these findings, we conducted a large randomized control trial on primary prevention of diabetes called the *'Diabetes Community Lifestyle Improvement Program (DCLIP)'* in individuals with prediabetes. We found that there was a reduction of as much as 32% in the incidence of diabetes in these subjects just by lifestyle modification plus Metformin (when indicated) in those with impaired glucose tolerance[16].

Are we achieving the goals of diabetes therapy?

Let us now address a more basic question. Are we achieving the glycemic and other targets in people

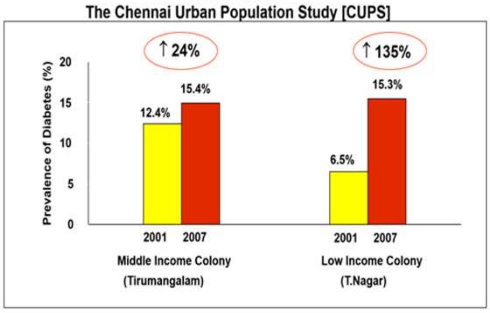
Figure 7 : PREVALENCE OF DIABETES IN RELATION TO PHYSICAL ACTIVITY



Mohan V, Gokulakrishnan K, Deepa R, Shanthirani CS, Manjula Datta. Diabet Med. 2005;22:1206-11

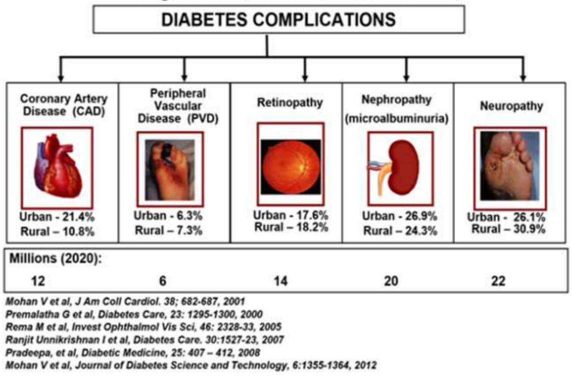
Figure 8 : NEW PREVALENCE RATES OF DIABETES IN THE STUDY POPULATION

The Chennai Urban Population Study [CUPS]



Mohan V et al, Journal of Diabetes Science and Technology 2011;5:918-927

Figure 9 : BURDEN DUE TO DIABETES



who already have diabetes? As part of the ICMR - INDIAB Study, we looked at statistics about glycemic control among people with self-reported diabetes in the country, and observed that only 31.1% of urban and 30.8% of rural population achieved good control of diabetes (HbA1c < 7%)[17]. The consequences of such poor control of the disease is reflected in the percentage of complications in the country, with nearly 1/3rd of both urban and rural populations going on to develop coronary artery disease, peripheral vascular disease, retinopathy, nephropathy or neuropathy. **(Figure 9)**.

Another of our studies published in *Lancet Diabetes and Endocrinology* recently highlighted the finding that only 7% of known individuals with diabetes in India were able to achieve the **ABC** targets of diabetes control, ie., **A**1c under 7%, **B**lood pressure below 140/90 mmHg and LDL **C**holesterol < 100 mg/dl **(Figure 10)**. This publication also presented

Figure 11 : 90 YEAR OLD SURVIVORS WITH TYPE 2 DIABETES

Figure 10 : THE 'ABC' TARGETS OF DIABETES THERAPY

A1c < 7.0%
BP < 140 / 90 mm Hg
Cholesterol - LDL cholesterol < 100mg/dl

state wise data with respect to physical activity, diet, glycemic and lipid profiles[18].

Is a long & healthy life possible for persons with diabetes?

I am often asked 'if one follows all the rules and keeps the ABC targets under control can people live long and healthy life despite diabetes?' In a paper we published in *Diabetes Care* in 2013[19], we reported, for the first time, data on long-term survivors with type 2 diabetes who had lived for 40 or even 50 years with diabetes and were doing well, with very few complications. When we looked into their detailed records, we found that the glucose control as shown by their A1cs were better, their blood pressure was fairly well controlled and their LDL cholesterol was also kept under control. This proves that if one follows the simple principles of diabetes treatment, it is possible to have a long and healthy life despite having the disease. In fact, it is very heartening that recently several of my patients have crossed the age of 90 years, and a few, even 100 years, something which would have been unimaginable a few decades ago. **(Figure 11)**

Take home messages

As the Indian diabetes epidemic marches on relentlessly, it is evident from the findings of several studies, that type 2 diabetes is eminently preventable and manageable. Though the country has undergone substantial nutrition transition, it is still not too late to go back to our roots and switch to healthier dietary patterns, using whole grains and legumes and eating more fruits and vegetables with higher fibre content. Reducing the carbohydrate intake to 40-50%, increasing protein to 20% of the total daily calorie intake, and getting the rest from healthy fats would help both in the prevention and control of diabetes. Physical activity is also very important. A multipronged strategy involving early diagnosis of diabetes, screening for its complications, and offering optimal therapy at all levels of care for those who already have diabetes (alongside primary prevention of diabetes in those with prediabetes) can help to reduce the economic burden due to diabetes in India and, importantly, protect the greatest resource of our country - its youth. The time to act is NOW!

Dr. V Mohan is the Chairman & Chief of Diabetology, Dr. Mohan's Diabetes Specialties Centre & Madras Diabetes Research Foundation, Chennai. The article is based on the Gopalan Oration of Nutrition Society of India delivered by him on 21.4.2022.

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Some concerns related to concurrent use of multiple strategies to combat iron deficiency

K Madhavan Nair

Introduction

Micronutrient malnutrition is prevalent across India mainly due to inadequate dietary diversity of habitual diets[1]. Well-established strategies to address micronutrient malnutrition include dietary diversification, food fortification, nutrition and health education, supplementation and public health measures. Food fortification has been identified as one of the safe and effective strategies to prevent and reduce the incidence of micronutrient deficiencies at a global. Alongside supplementation, food fortification was also an important move that India had embarked on for reducing the micronutrient inadequacies in the diets of the populations[2].Currently, there is an ongoing debate on the deficiencies of iodine, iron, vitamin A, vitamin D and anemia among children and adolescents under 19 years of age in the light of outcomes of a few research papers that assessed the data from the recent comprehensive national nutrition survey (CNNS) using state-of-the-art methodology of analysis[3]. Further, the nutrient reference values for Indians have undergone revision by the ICMR-NIN in 2020[4]. In the light of the above, there is a need to contextualize current public health strategies to prevent and control micronutrient deficiencies among our populations. Concerns have been raised with respect to the simultaneous implementation of food fortification and supplementation for iron which may be associated with adverse health consequences[5].

Estimated Average Requirement (EAR) as the Nutrient reference values of iron for public health nutriton:

The ICMR-NIN expert committee report on Nutrient requirements of Indians (2020)[4] which provides three reference values for nutrients viz. estimated average requirement (EAR) the recommended dietary Allowance (RDA=EAR+2SD) and tolerable upper limits (TUL) for all micronutrients as against the earlier single reference value for RDA provided in ICMR NIN report on RDA for Indian[6]. The current standards for fortification had been computed based on RDA for Indians ICMR-NIN 2010. If one peruses the Table 1, it is obvious that there exists a considerable difference between the EAR and RDA for iron provided in ICMR NIN 2020 and the RDA provided in ICMR-NIN 2010. The range of EAR for iron varies from 6 mg per day for infants 1-3 y to 21 mg for pregnant women in ICMR-NIN 2020, as against the range of RDA of 9mg/day for infants 1-3 yr to 35 mg/day for pregnant women recommended in 2010 Also, the prevalence of inadequate iron intake (PIA) is lower when the current EAR values for iron are taken into account. Based on this concept the PIA gap for iron may not be high enough to justify layering of multiple strategies to combat iron deficiency and anaemia[5].

Iron folic acid (IFA) supplementation programme in India

The National programme of IFA supplementaion has undergone several modifications; currently life-cycle approach for IFA supplementation and fortifed foods (double fortifed salt and staple foods fortifed with iron) arebeing implemented in India (Box 1)

Iron dose, dosing and low-grade inflammation

A good compliance with iron folate supplementation provided under the National programme for anemia control is of paramount importance to achieve significant reduction in anemia due to iron deficiency. High dose iron is known to produce gastric disturbances; this minor but troublesome side effect is a leading cause of low compliance. Habitual Indian diets are rich in phytates and polyphenols; absorption of high doses of iron consumed after meal may be very low. A recent systematic review as part of the National consultaion have recommended use of lower dose of IFA for prophylaxis[7]. Accordingly, the dosage has been reduced from 100 mg of elemental iron to 60 mg for adults and 45 mg for adolescents.

Role of hepcidin in iron bioavailability:

Hepcidin is the key regulator of systemic iron balance acting in unison with intracellular iron metabolism.

Box 1 MILESTONES OF IRON SUPPLEMENTATION PROGRAMME IN INDIA
➢ The Nutrition Society Constituted an Expert Committee in 1968. Based on its recommendations the national anaemia prophylaxis programme was initiated:
➢ 1970: Inception of National Nutritional Anaemia Prophylaxis Programme (NNAPP) for pregnant and lactating women and children 1-11y through PHCs: 60mg iron and 0.5mg folic acid daily for 100 d (pregnant women), 20mg iron and 0.1 mg folic acid daily for 100 d (children)
➢ 1990: Evaluation of NNAPP, poor coverage, with only 19 % among pregnant women and 1% in children. Poor monitoring, poor compliance and lack of screening were detected. Renamed as the National Anaemia Control Programme, the emphasis was on screening for anaemia and improving coverage. The dosage was changed to 100 mg iron in pregnancy. Those with Anaemia received 2 tablets.
➢ 2002 NNMB and DLHS 2000 survey data became available, and showed improved coverage of 63 % among pregnant women
➢ NFHS-3 2005-06: The coverage had improved to 65 % among pregnant women. The haemoglobin test was introduced for ever-married women and their children below 3 y for anaemia and assessed by Hemo Cue Instrument. The number of states with anaemia prevalence below 40% -3 states, 40-60% -16 states and 60-75% --9 states.
➢ 2007: Review of policy regarding iron + folic acid by the Government of India (Dept. of Health and Family Welfare): Inclusion of infants, school children and adolescents under the programme, turning it into a life cycle approach programme.
➢ 2013: Renamed as National Iron Plus Initiative (NIPI), retaining the life cycle approach. Tie-up with NRHM. Targeted approach for identifying persons with anaemia, and a mass programme of IFA supplementation for others where screening is not carried out.
➢ 2015-16: NFHS-4 data, Anaemia in children 6-59 mths 58%; Women 15-49 yrs 53%; Men 29%
➢ 2018: Anaemia Mukt Bharat (AMB) programme to accelerate the decline of anaemia in various age groups by intensifying strong initiatives to further strengthen the already present mechanisms as well as develop new ones to reduce anaemia. Six interventions were recommended: (https://anemiamuktbharat.info/home/interventions)
ophylactic iron and folic acid (IFA) supplementation: Biweekly 20 mg iron+100µg folic acid syrup for children 6-59 mths; Weekly, 1 IFA tablet containing 45 mg iron + 400 µg Folic Acid for 5-9 yrs children; Weekly, 1 IFA tablet containing 60 mg Iron + 500 µg Folic Acid for10-19 yrs adolescent boys and girls; Weekly, 1 IFA tablet containing 60 mg Iron + 500 µg Folic Acid 20-49 yrs WRA; Daily, 1 60 mg Iron + 500 µg Folic Acid, tablet starting from the 4mth of pregnancy, continued throughout pregnancy (minimum 180 days during pregnancy) and to be continued for 180 days, post-partum.
eworming
tensified year-round behavior change communication campaigns such as (i) Compliance with IFA supplementation and deworming; (ii) Appropriate Infant and Young Child Feeding (IYCF) with emphasis on adequate and age-appropriate complementary foods for children 6 months and above; (iii) Increase in intake of iron-rich, protein-rich and vitamin C-rich foods through dietary diversification/quantity/frequency and food fortification, and (iv) Promoting the practice of delayed cord clamping (by at least 3 minutes or until cord pulsations cease) in all health facility deliveries followed by early initiation of breastfeeding within 1 hour of birth.
sting and treating of anaemia, with focus on pregnant women and school-going adolescents –therapeutic management of anemia
landatory provision of IFA, fortified foods in government-funded health programmes. The Government of India has mandated the use of fortified salt, wheat flour and oil in foods served under ICDS and MDM schemes. In addition, all health facility-based programmes where food is being provided are mandated to provide fortified wheat, rice (with iron, folic acid and vitamin B12), and double fortified salt (with iodine and iron), and oil (with vitamin A and D) as per standards for fortification of staple foods (FSSAI, 2016)
tensifying awareness, screening and treatment of non-nutritional causes of anaemia in endemic pockets with special focus on malaria, haemoglobinopathies and fluorosis.
➢ NFHS-5 2019-21: Anaemia prevalence - Children 6-59 mths 67%; Adolescent Girls 15-19 yrs 59%, Adolescent boys 15-19 yrs 31%, Women of Reproductive age 57%, Pregnant women 52% and non-pregnant 57%.

Iron supplementation acutely increases the circulating plasma hepcidin level. Plasma hepcidin negatively correlates with iron bioavailability and has a circadian increase over the day. Morning iron supplementation enhances this increase in plasma hepcidin, potentially affecting iron absorption from supplements given as divided doses in the morning and in the afternoon. Further, the impact of iron supplementation on iron status is debatable.

A recent RCT has reported higher serum hepcidin levels after consecutive iron dosing compared to alternate-day dosing, suggesting hepcidin-mediated inhibition of supplemental iron absorption. The study concluded that percent iron absorption in iron-deficient women is highest at low iron doses (40 mg) and that, consecutive-day dosing decreased iron bioavailability. These observations further emphasize the need to study longer-term, intermittent iron supplementation and suggest that low-dose iron may maximize iron absorption, increase dosage efficacy, reduce gastrointestinal exposure to unabsorbed iron, and ultimately improve tolerance of iron supplements.

Role of inflammation

The role of inflammation in iron homeostasis is proposed to be mediated through internalization, ubiquitination, and subsequent lysosomal degradation of ferroprotein by hepcidin in enterocytes, hepatocytes, and macrophages leading to hypoferremia. Studies have shown the possibility of a systemic low-grade inflammatory state in target groups and influencing the dynamics. We have tested psychological stress mediated low-grade inflammation and changes in iron status among adolescent boys. A path analysis was carried out to test for the relationship between stress-IL-6-hepcidin axes[8]. We could establish a direct relationship between adolescent life-event stress and inflammatory markers as well as hepcidin but these changes have not led to hypoferremia, suggesting that this interaction may not influence iron homeostasis in adolescent boys. However, such studies are to be undertaken among preschool children who are more susceptible to infection.

Further, absorption studies with low dose (30 mg) iron taken during fasting by men and women of different iron status strongly suggest that build-up of iron stores was much lower from iron supplements than from dietary iron[9]. Thus, targeting dietary iron as a strategy would be more beneficial than high doses of iron supplements for building iron stores during childhood. This may also protect gut health from iron-mediated ill effects among vulnerable segments of the population.

Response of iron biomarkers to supplemental and fortificant iron

IFA supplementation in iron deficient population is expected to bring about improvement in iron biomarkers. But NFHS -5 reported a higher prevalence of anemia when compared to NFHS 4. The reason for this has not been clearly understood. This could be due to problems in methods used for Hb estimation. Some studies have reported that response of iron biomarkers to iron supplementation and fortification among vulnerable segments of the populations may not be consistent and uniform.

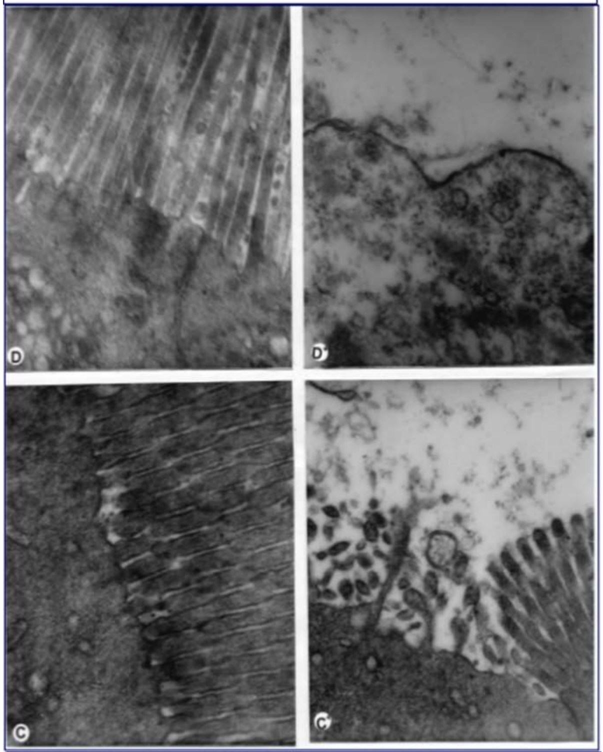
The response of 60 mg iron+0.5 mg folic acid for 100 days on biomarkers of iron, hemoglobin, serum ferritin, transferrin receptor was investigated in pregnant women[10]. The results suggested that supplementation improved Hb levels (9.6 to 11 g/dL) in anemic mothers. Among non-anemic mothers there was a reduction in mean hemoglobin (12.2 to 11.6 g/dL) but mean serum ferritin showed an increase (ferritin 12.8 to 20.3 µg/L) suggesting preferential accumulation of storage iron in the body.

A double-blind, placebo-controlled trial was conducted in Hyderabad among 5–11-y-old schoolchildren (n=140) who were randomly assigned to receive either fortified rice (19 mg iron) or unfortified mid-day meal for 8 months. Regular intake of fortified rice improved iron stores and reduced iron deficiency but did not reduce anemia[12]. A similar study conducted in Bangalore also reported improvement in iron stores and reduction in iron deficiency[11].

The above studies clearly indicated that these interventions have not made an impact on the prevalence of anemia. It is possible that this could be due to interplay of both the dietary and host factors. While host factors are important, the intervention among preschoolers using dietary approach seems to uniformly impact all the biomarker of iron status This directional change could be due to low iron load and higher absorbability of dietary iron brought about by vitamin C rich fruit, guava enhancing absorption of iron by more than 2-3 times[12,13]. Also, the food and nutrient synergy created established a perfect iron homeostasis mechanism.

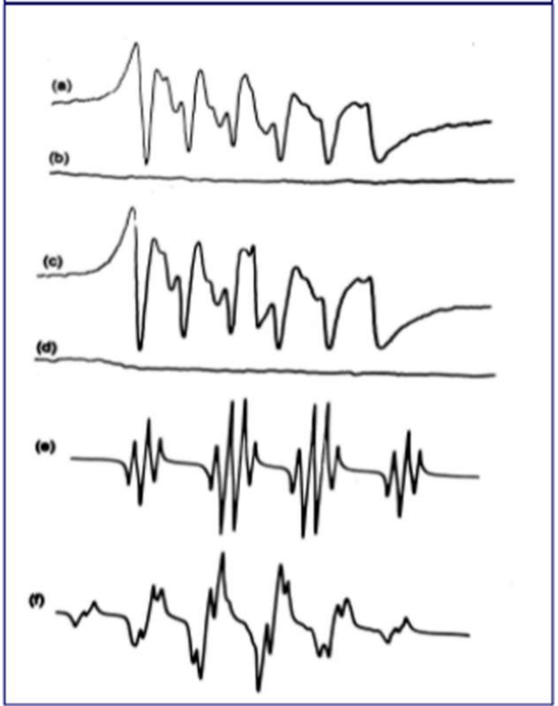
Iron Excess

Fig 1 Transmission electron micrographs of rat intestinal absorptive cells



C control D iron deficient rats both with intact micro villi C+ control rats and D+ deficient rats both given oral iron for 15 days with eroded sparse microvilli

Fig 2 EPR spectrum of radical adducts



a) mucosa with iron, b) mucosa without iron; c) lumen with iron; d)lumen without iron; e) computer simulated experimental spectrum; f) spectral simulation of experimental spectrum of a second species

The tolerable upper limits (TUL) of iron are 45 mg/day for adults and 40 mg/day for children. The TUL is about 2 (pregnant women) to 7 (1-3 yr children) times the EAR of respective gender and age sub-groups of the healthy population. Considering limited absorption of iron and a highly regulated process, a large fraction of the iron supplement administered daily remains unabsorbed in the small intestine. The concerns with respect to this unabsorbed iron are:

(1) Iron can be very toxic by forming reactive oxygen species (ROS), generated through the Fenton and Haber–Weiss reaction (Box-2). The highly reactive hydroxyl ion OH^- induces severe damage to enterocyte cells and their constituents, lipids, proteins and DNA.

(2) In biological system iron rarely exists in free form and is always tightly bound to proteins/ligands limiting supply to potential pathogens in the body. Availability and abundance of sequestering system in the gut is not well documented and therefore, the consequences on gut health need extensive investigation.

The above issues are especially important in the context of nutritionally compromised-oxidant rich and antioxidant depleted environment with low grade inflammation among the vulnerable segments of our population. These are risk factors which are not generally considered in programmatic level of IFA supplementation.

Basis of intermittent iron supplementation:

Though there is evidence of a positive impact of iron supplementation and fortification in well designed and conducted clinical trials from developed countries, the results obtained with large scale public health programmes in developing countries have been variable[14-17]. Factors including low

BOX-2: Fenton and Haber–Weiss reaction

Fenton reaction:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^- \quad (1)$$

Iron reduction:

$$Fe^{3+} + O_2^{-} \rightarrow Fe^{2+} + O_2 \quad (2)$$

Haber–Weiss reaction, in the presence of catalytic amounts of iron (sum of 1 and 2):

$$O_2^{-} + H_2O_2 \rightarrow O_2 + {}^{\bullet}OH + OH^- \quad (3)$$

compliance have been attributed to the variable responses to iron supplementation in public health programmes in developing countries. However, it is unclear to what extent the failure of such programmes is due to the response of the intestinal absorptive surface to repeated high doses of iron.

In a series of studies in rodent models we have shown the consequences of excess iron on absorptive sites[18-21]. Earlier studies have shown that repletion of iron deficient rodent with iron promotes oxidative stress, damages the absorptive cells and brings about functional and ultrastructural derangements in the intestine. The causative factor responsible for such effects was identified as the hydroxyl radical produced by excess iron at the site of iron absorption (Figure1 & 2). The findings on the role of food per se (natural diet) in reducing the effects of iron mediated oxidative stress have practical relevance[22].

Studies conducted in rodent models to elucidate the protective effects of antioxidants (alpha-tocopherol/ascorbic acid and zinc) on iron mediated oxidative damage of the gastrointestinal tract is summarized below.

Oral administration of iron alone or in the presence of alpha-tocopherol and or ascorbic acid or zinc per day for 15 days was carried out in iron depleted animals and the protective role studied[20,23-25]. We demonstrated that administration of iron along with antioxidant normalized functional integrity and had significantly elevated levels of antioxidants suggesting that co- administration offered effective protection and reversed all key iron mediated adverse effects.

Co-localisation studies at the absorptive surface have revealed that iron accumulates at the site of absorption during iron repletion which may block its absorption from subsequent doses. In another study we tested the sequential changes using tandem immunohistochemical staining of iron dependent proteins ferritin, transferrin and transferrin receptor in rodent model and human intestinal biopsies. It was observed that the directional change in staining intensity (high ferritin with low transferrin receptor in iron excess a reciprocal relationship in iron deficient condition) was in conformity with the iron status[21].

Less frequent regimens of iron supplementation, such as once weekly or twice weekly with iron alone or in conjunction with folic acid, have been evaluated in the last decade as a promising innovative regimen. The weekly iron administration is based on two lines of evidence: (1) daily iron supplementation, by maintaining an iron-rich environment in the gut lumen and in the intestinal mucosal cells, produces oxidative stress, reduces the long-term iron-absorption efficacy and is prone to increasing the severity and frequency of undesirable side effects[18,20,26,27] (2) the concept that exposing intestinal cells to supplemental iron less frequently, every week based on the rate of mucosal turnover that occurs every five to six days in the human, may improve the efficiency of iron utilization. Current strategy includes weekly and biweekly iron folic acid supplements to vulnerable segments of the population as part of Anemia Mukt Bharat (Box-1).

Conclusions

Greater emphasis on simple dietary approach can be implemented through the nutrition sensitive food-based platforms available as part of national programmes in India for improving bioavailability. Inclusion of fruits rich in vitamin C such as guava has the potential to meet the required molar ratio of vitamin C for doubling iron absorption from habitual diets. These approaches satisfy the iron requirement in all vulnerable segments of the population and suggested to include as a core strategy to reduce anemia. ICMR-NIN has operationalised the use of Estimated Average Requirement (EAR) as the metrics for iron requirement. There is need to understand its application to the assessment of population level adequacy or inadequacy of iron and designing appropriate National strategies to increase iron intake.

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The 45th Gopalan Memorial Oration was delivered by Dr. V. MOHAN, Chairman & Chief of Diabetology, Dr.Mohan's Diabetes Specialties Centre & Madras Diabetes Research Foundation, Chennai, on 21.04.2022 on virtual mode on the topic "The diabetes epidemic in India: some lessons learnt"

NUTRITION NEWS

The 33rd Dr. Srikantia Memorial Award Lecture was delivered by Dr Avula Laxmaiah, Scientist G, National Institute of Nutrition, Hyderabad on 10.06.2022 on virtual mode on the topic "Time trends in triple burden of malnutrition in India – Pilot intervention models for low- and middle-income countries

The 12th Dr. Rajammal P Devdas Memorial Award Lecture was delivered by Dr. Bharati Kulkarni, Scientist G Indian Council of Medical Research, New Delhi on 10.06.2022 in virtual mode. The topic of the lecture was "Iron nutrition and anemia in India: some insights from recent research."