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Original Research Article

A RETROSPECTIVE STUDY ON NON-ALCOHOLIC FATTY LIVER DISEASE PATIENTS ON VERY LOW CALORIE DIET.

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) ranges from non-alcoholic fatty liver to non-alcoholic steatohepatitis. Weight loss is one of the advised therapies for NAFLD patients in the absence of any pharmaceutical treatment therefore this observational study retrospectively analyzes 30 NAFLD adult patient's data with the objectives to assess the nutritional status of the NAFLD patients and check the efficacy of a very low calorie diet(VLCD) to achieve weight loss in patients with NAFLD. The retrospective data at admission of the patients included their anthropometric measurements, biochemical parameters, fatty liver evaluation through radiological examination and 24 hour dietary recall. Weight change record after the patients followed VLCD for 15 days was taken from the records and analyzed using paired student t test.

The findings from the study indicated the patient's dietary consumption before following VLCD was higher than the estimated average requirement (EAR) for energy and the carbohydrate and fat consumption was higher than their recommended dietary allowance (RDA) but the protein consumption was low as per the RDA. The majority of the patients were obese (Grade II). Overall 3.32% weight reduction in the subjects was observed after following the very low calorie diet. Significant reduction in the weight was found in those subjects who followed the very low calorie diet ($p=0.00$). NAFLD patients following VLCD achieved rapid weight loss and further this weightloss can help in improving their liver health and quality of life of the NAFL Dpatients.

Key terms : NAFLD, VLCD, obesity, overweight, weight loss

INTRODUCTION

NAFLD is the accumulation of extra fat in liver cells whose primary cause is not alcohol. In some individuals, NAFLD may further lead to liver inflammation, liver fibrosis, liver cirrhosis and liver cancer. Fatty liver is when more than 5% of the liver weight is fat (1).NAFLD includes characteristic histological conditions: non alcoholic fatty liver (NAFL) and non alcoholic steatohepatitis (NASH) (2). NAFLD is the foremost cause of severe

liver diseases nationally and internationally, research shows that 25% of the global adult population ranging from 13.5% in Africa to 31.8% in the Middle East is affected from NAFLD. NAFLD is emerging with higher prevalence in those with overweight or obese and those with diabetes or pre-diabetes(3).According to National Family Health Survey (NFHS) 5 data the obesity in Indian women and men has increased to 3.4% and 4% respectively as compared to NFHS-4 data (4). According to a study published in Journal of Clinical and Experimental Hepatology, one in three adults or children have NAFLD in India(5).The treatment guidelines for NAFLD from the American Association for the Study of Liver Diseases (AASLD) to improve liver steatosis a weight loss of 3 to5% should be there(6).

A very low-calorie diet (VLCD) produces rapid weight loss and preserves lean body mass by providing below 800Kcals, 50-80gm protein and 100% of the recommended intake for vitamins and minerals per day, to promote rapid and significant weight loss (7). Various studies have shown that VLCD intervention on 2 weeks can help in reducing the weight loss (8,9). VLCD is currently the most effective non-pharmacological, non-surgical approach to weight loss in the obese population.Despite of several active researches in this field, the awareness about the role of VLCD in reducing fatty liver in NAFLD patients in India is still not clear. Therefore, different observational and experimental studies should be conducted in the rural and urban parts of India to identify its significant role which would help in making future strategies in improving the health of the patients through this diet intervention. So, the present study is designed to check the efficacy of a very low calorie diet to achieve weight loss in patients with NAFLD.

MATERIAL AND METHODS

This study was carried out in retrospective mode with 30 patients. In this study 1 month data of NAFLD patients who were prescribed VLCD with a meal replacer-for 15 days from August 2021 to September 2021 was retrieved from the outpatient department (OPD) records of Center of Liver and Biliary Sciences (CLBS), of Max Super Specialty Hospital, Saket, NewDelhi with the objectives to check the efficacy of a very low calorie diet to achieve weight loss in patients with NAFLD. The samples were selected through following inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria:
• Non alcoholic fatty liver disease patients • Gender- male and female with no co-morbidities • Age group- 18 to 60 years old • Body mass index (BMI) higher than 27 kg/m^2	• On anti-obesity drugs • International patients were excluded • Patients with other disorders like cancer and renal patients • Diagnosed eating disorder or purging • pregnant/considering pregnancy

Ethical approval: The Institutional Scientific Committee (ISC) and The Institutional Ethics Committee (IEC) [Max Healthcare Ethics Committee (MHEC)] reviewed and discussed the study and gave approval to conduct study at Max Super Speciality Hospital, Press Enclave Road, Saket, New Delhi-110017. Waiver of consent was obtained from MHEC.

Data Collection

Retrospective data about socio-demographic profile, anthropometric measurements included Height (in cm) and weight (in Kg). BMI (Kg/m^2) was further calculated through height and weight of the subjects. Biochemical assessment of the subjects was done by determination of Bilirubin (Total), SGOT, SGPT, Total protein, Globulin, Albumin, Lipid Profile Cholesterol Triglycerides, LDL, HDL, VLDL in blood sample. Fatty liver grade measurement was assessed through FibroScan, Computed Tomography (CT), Magnetic ResonanceCholangiopancreatography (MRCP), Ultrasound Sonography test (USG) Abdomen. 24 hour dietary recall was used for assessment of dietary intake of macronutrient and energy consumption. The retrospective data of pre and post-weight change of NAFLD patients was collected from records. These patients were prescribed VLCD with meal replacer (100g) along with consumption of complex carbohydrates, non-starchy vegetables, fruits, pulses and 2-3 liters of fluid daily, providing 1200 Kcal/day. This was done by replacing breakfast and dinner with meal replacer for 15 days. The type of sampling used in the study was purposive sampling. The meal replacer was not funded by any company for the study.

Energy and macronutrients composition of meal replacer per 100g

Energy and macronutrients	Value
Energy (Kcal)	403
Protein (g)	38
CHO(g)	36.9
Fat(g)	11.5

The data was collected from the Out Patient Department records from August 2021 to September 2021 the patients diagnosed with NAFLD (existing and diagnosed for the first time) through imaging study suggestive of NAFLD or confirmed by the consultant from the OPD of Center of Liver and Biliary Sciences of Max Super Speciality Hospital, Saket.

Data analysis

The analysis was done on STATA software version 13.1.Tosummarize the descriptive statistics- mean and

standard deviation was calculated. Paired Student's t- test was used for analysis. A significance level of the results was established at $p < 0.05$.

RESULTS AND DISCUSSION

Demographic data of the subjects was collected, and it was found that majority of the subjects (63.34%) were males and mean age of the subjects were 39 years. Sixty percent of the subjects were graduate and 63.3% were doing skilled occupation. Majority of the subjects (80%) were married.

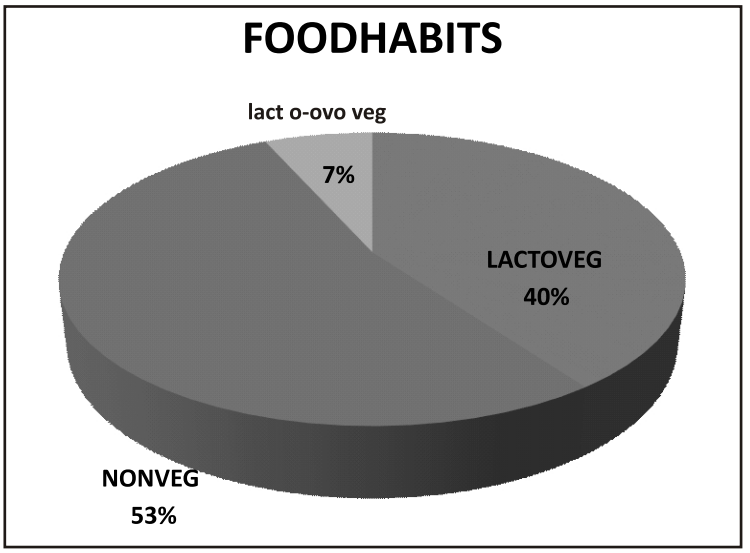

Figure1: Food Habits of the subjects

Food habits play an important role as they are the modifiable risk factor that plays an important role in the prevention or delaying non-alcoholic fatty liver disease (NAFLD). Figure-1 depicted that more than 50% of the subjects were non vegetarian. Similar results have been shown in studies that consumption of non vegetarian foods has been associated with the prevalence of NAFLD (9).

Table1: Anthropometric measurements of the subjects prior to Nutritional Intervention

S. No.	Subjects	Height(cm)	Weight(kg)	BMI (kg/m^2)	Grade of obesity
		Mean±SD			
1	Male(n=19)	172.63± 8.99	92.64± 12.89	31.02± 2.95	Grade II
2	Female(n=11)	156.27± 9.20	78.32± 9.85	32.00± 2.39	Grade II
3	All subjects(n=30)	166.63± 9.44	87.39±12.84	31.38± 3.03	Grade II

BMI Source- Misra et.al 2009; Indian consensus. Grade 1 obesity- 25- 29.9kg/m2: Grade 2 obesity- 30-34.9Kg/m2: Grade 3 obesity- >35Kg/m2

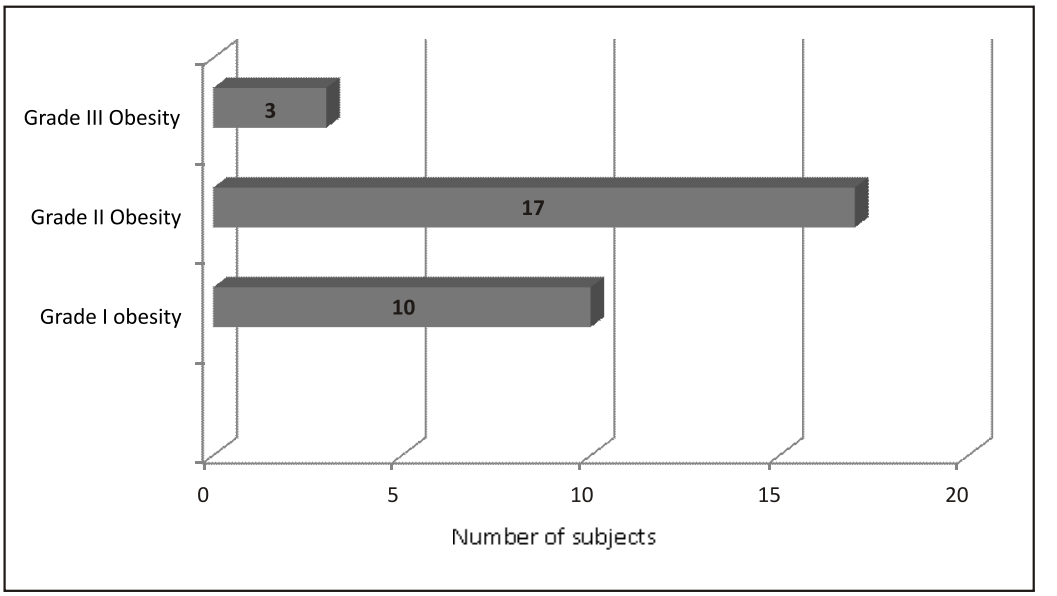

Figure-2 Distribution of the subjects based on BMI

More than 50% of the subjects suffer from Grade II Obesity (BMI-30-34.9Kg/m2) as per Misra et al 2009 source of classification. The similar finding was reported in–a study published in the Journal Gastroenterology Research and Practice (10).

Table 2: Energy and macronutrients consumption of the subjects prior to Nutritional Intervention

Energy/ macronutrients	Male (n=19)			Female (n=11)		
	RDA/ EAR2020	Consumed (Mean±SD)	Difference	RDA/ EAR2020	Consumed (Mean±SD)	Difference
Energy(Kcal)	2110(EAR)	2305 ± 702.65	+195	1660(EAR)	1810±249.78	+210
Protein(g)	54	42.58 ± 12.50	-11.42	46	37.05 ± 6.66	-8.95
Carbohydrate (g)	130	237.21± 41.20	+107.21	130	202.37± 31.85	+72.37
Fat(g)	25	63.90 ± 27.21	+38.9	20	59.68 ± 19.00	+39.68

RDA- Recommended Dietary Allowance, EAR- Estimated Average Requirements:Nutrient Requirements for Indians, A report of expert group, ICMR 2020

We recorded retrospective 24hr dietary recall data for all patients before following VLCD. This data depicted 81.8% females and 52.6% males were consuming more energy than the EAR 2020.The majority of the calorie-intake was met by the consumption of refined cereals, saturated fats and trans-fats.

However, 90.9% female and 84.2% males were consuming less protein than the recommended dietary allowance (RDA 2020) of protein. Studies have indicated that protein deficiency and malnutrition can lead to NASH development whereas high protein and low carbohydrate diet decreases liver steatosis by inhibition of *de novo* lipogenesis (11).

It was also observed that all the patients were consuming more carbohydrates, mostly as refined cereals and simple carbohydrates, than the recommended dietary allowance (RDA 2020) of carbohydrate. Consumption of soft drinks rich in fructose contributes to insulin resistance and NAFLD development. Fructose intensifies lipogenesis and triglyceride synthesis (12). It was seen in the patients dietary recall data that the major consumption of fats consisted of trans-fats and saturated fat. Intake of saturated fats increases LDL and triglyceride levels in the patients, therefore it is recommended that NAFLD patients consume fats rich in polyunsaturated fatty acids and mono unsaturated fatty acids. Dietary recommendations for NAFLD suggest avoidance of trans-fatty acids contained in highly processed food products (13).

Table 3: Liver Function Test of the subjects prior to Nutritional Intervention

Liver Function Test Mean ± SD		**Reference Value**
Bilirubin(T) (mg/ dL)	**0.95 ± 0.79**	0.3-1.2
SGOT (U/L)	**48.8** ± 23.072	<35
SGPT (U/L)	**66.01** ± 35.32	<35
Total protein (g/ dL)	7.40 ± 0.62	6.6-8.3
Albumin (g/ dL)	4.01 ±0.89	3.5-5.2
Globulin (g/ dL)	2.82 ± 0.68	2.3-3.5

Table 4: Lipid profile of the subjects prior to Nutritional Intervention

Lipid Profile Mean ± SD		**Reference Value**
Cholesterol (mg/dL)	**200.4** ± 36.68	<200
Triglycerides (mg/dL)	140.91 ±50.41	<150
LDL(mg/dL)	**126.9**± 28.53	<100
HDL(mg/dL)	42.14 ± 8.22	>40
VLDL(mg/dL)	29.28 ±10.69	<30

Table 5: Other tests of the subjects prior to Nutritional Intervention

Test	Mean ± SD	Reference value
Hemoglobin(gm%)	**12.76 ± 2.92**	12-15
HbA1C(%)	**6.01%** ± 1.42	<5.7

SGOT- Glutamic oxalacetic transaminase, SGPT- Glutamic pyruvic transaminase
LDL- low density lipoprotein, HDL- high density lipoprotein, VLDL- very low density lipoprotein
Source- Apollo Hospitals Group, Dept of Dietetics The best of Basics in Clinical Nutrition- Deietetian's essential pocket book Fourth edition- 2016
HbA1c- Glycated hemoglobin
Source- Apollo Hospitals Group, Dept of Dietetics The best of Basics in Clinical Nutrition- Deietetian's essential pocket book Fourth edition- 2016 and ADA, 2018

Before consuming VLCD diet SGOT and SGPT were raised (table 3), cholesterol was borderline high, and LDL (table 4) and HbA1C (table 5) were also high in the patients. Very low calorie diets (VLCDs) have demonstrated to be a viable treatment strategy for people with type 2 diabetes mellitus (T2DM). VLCD enables sustainable weight loss in those patients who are completing the intervention. Improvement in liver health, reduction in the risk of cardiovascular diseases, and enhancement in quality of life were demonstrated in patients who consumed very low calorie diets (11).

Table 6: Radiological examination before consuming VLCD diet

Fatty liver grade measurement	Frequency	Percentage
Fibro Scan • Grade II	5	16.6%
CT(Computed Tomography) • Grade II	5	16.6%
MRCP(Magnetic Resonance Cholangiopancreatography) • Grade II • Grade III	6 1	20% 3.3%
USG Abdomen (ultrasound sonography test) • Grade II	13	43.3%

Table 6 indicates majority of the patients (96.6%) had Grade II fatty liver. In a study published in advanced biomedical research it was found that majority of the NAFLD population was grade II fatty liver (14).

Table 7: Weight change in the patients after following VLCD diet

	Pre weight	Post weight	Percent weight change	**P-value**
All subjects	87.39	84.48	3.32%	0.00

The results of the study indicated that there was 3.32% weight reduction in the participants after following the very low calorie diet (Table 7).

For statistical analysis t-test was applied and it was found that at 0.05 level of significance there is significant reduction in the weight of the patients who followed the very low calorie diet(p=0.00).

CONCLUSION

In this study significant reduction in the weight of the patients was observed who followed the very low calorie diet (p=0.00).In nut shell very low calorie diet will be helpful for liver heath.

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Original Research Article

EFFECT OF DIETARY INTERVENTION IN GESTATIONAL DIABETES PATIENTS.

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ABSTRACT:

Background: Gestational diabetes mellitus (GDM) is defined as a glucose tolerance disorder with onset or first recognition during pregnancy. GDM is associated with several adverse maternal and neonatal outcomes. Management to reduce the incidence of GDM could decrease the incidence of these complications. The vital issue In GDM prevention is the implementation of proper dietary patterns, appropriate physical activity, and a combination of diet and lifestyle modifications. However, intervention studies examining the effects of diet and lifestyle on GDM prevention are contradictory. The aim of this study was to review the scientific evidence on nutritional intervention strategies, including diet and physical activity that are effective in reducing the risk of GDM. The presented article is a narrative review. This article indicates that certain nutritional factors may have significant benefit in preventing GDM.

Objectives:

☐ To improve Nutritional status by creating awareness in GDM patients through Nutritional education.

☐ To improve haemoglobin levels and also to decrease blood glucose levels in GDM Patients.

Methodology: The study was conducted on 30 Pregnant GDM subjects (control) and 30 Pregnant GDM subjects (experimental) from Department of Obstetrics & Gynaecology in SVS Medical College Hospital. Age of the subjects varies from 20 years to 35 years. All cases had clinical and laboratory evidence of GDM. Specific questionnaires were prepared and used to collect medical, dietary history and knowledge of the patients on food and glucose levels. Clinical values of Random Blood glucose Levelsand Haemoglobin levels were obtained prior and post intervention (6 months of intervention). The data thus collected was computerized in a specific program developed on Microsoft Excel 2010 software. The database so prepared was analysed with the help of statistical analysis, t-test, p-test and the results were transferred to predesigned classified tables, bar diagrams and pie diagrams prepared according to the aims and objectives of the study.

RESULTS: The obtained data showed that the mean value of glucose levels Glycated Haemoglobin (HbA1c) and General Random Blood Glucose(GRBG) in post nutrition education program was highly significantly ($p<0.0001$) decreased than prior nutrition education program whereas there was no significant change in control group. The data also showed that the mean value of Haemoglobin was significantly improved in post nutrition education program whereas there is no significant change was observed in the control group.

CONCLUSION: The above parameters indicates that there is an urgent need for dietary intervention using nutrition education program for improving knowledge and skills in nutritional practice of GDM patients. Therefore, nutritional counselling by qualified dieticians should be mandatory in GDM patients as part of the medical therapy.

KEYWORDS: Gestational Diabetes Mellitus(GDM), Glycated Haemoglobin (HbA1c),General Random Blood Glucose (GRBG).

INTRODUCTION: GDM is one of the most common complications in pregnancy. Women with GDM and their offspring are at increased risk of short and long term complications, including, for mothers later development of T2DM(Type 2 Diabetes) and CVD(Cardio Vascular Disease), and for offspring, increased lifelong risk of obesity, T2DM, and metabolic syndrome. HAPO (Hyperglycaemia and Adverse Pregnancy Outcome) study established a continuous relationship between maternal hyperglycaemia and adverse outcomes and a one-step approach for the diagnosis of GDM using a75-g 2-h OGTT (Oral Glucose Tolerance Test) was proposed. Recently, the HAPO follow-up study has also shown HPL (Human Placental Lactogen)a continuous association between maternal glucose levels in pregnancy and late childhood glucose and insulin resistance, independent of maternal and childhood BMI(Body Mass Index) and family history of diabetes. The new criteria have been adopted by several societies, including the American Diabetes Association, the Endocrine Society and WHO (World Health Organization).This dramatic increase in GDM diagnosis, together with higher rates of obesity, sedentary lifestyle, and older age at pregnancy -all risks factors related to GDM has become a growing health problem demanding preventive strategies.

The idea of preventing GDM with diet is very attractive. However, studies show conflicting results depending on the type of nutritional intervention and the moment of its implementation. In addition, most studies have included only women with high risk of developing GDM[1].

Physiologically, during pregnancy insulin sensitivity progressively decreases until the second trimester, declining by 50%60% compared with pre-pregnancy values. Insulin sensitivity is influenced by the increase in adipose tissue, and by the release of hormones, such as estrogens and progesterone, or placental factors, such as HPL. In

particular, HPL has a lipolytic effect, leading to the rise in circulating fatty acids. Consequently, maternal metabolism is shifted towards a greater use of lipids rather than glucose as an energy source, which is necessary to give the fetus an adequate glucose reserve. Insulin resistance develops as a consequence of high maternal circulating fatty acids. Contextually, insulin secretion is implemented to balance peripheral insulin resistance. However, if the increase in pancreatic β-cell secretion is not able to compensate insulin resistance, diabetes occurs. Moreover, physiological pregnancy is characterized by low grade inflammation, which is exacerbated in GDM. Thus, insulin resistance might develop from this pro-inflammatory state.

The main risk factors for GDM are pre-pregnancy body mass index (BMI) in the range of overweight or obesity, High Maternal Age, and first degree family history of T2DM[2].Gestational diabetes mellitus (GDM) is a common obstetric condition with a high incidence rate among pregnant women.[3,4,5]

The diet recommended for women with GDM should contain sufficient macronutrients and micronutrients to support the growth of the foetus and, at the same time, limit postprandial glucose excursions and encourage appropriate maternal gestational weight gain. Blood glucose excursions and hyperglycaemic episodes depend on carbohydrate-intake. Therefore, nutritional counselling should focus on the type, amount, and distribution of carbohydrates in the diet. Further, physical activity has beneficial effects on glucose and insulin levels and it can contribute to aimproved glycaemic control[6]. GDM increases the risk of suboptimal maternofoetal outcomes and is associated with pre-pregnancy obesity and excessive gestational weight gain[7, 8,9,10].

Materials and methods: This was an intervention study to evaluate the effect of dietary intervention in subjects with gestational diabetes with their consent. The study was conducted in SVS Medical College hospital from Department of Obstetrics and gynaecology. Age of the subject varies from 20 years to 35 years. The Pregnant GDM women were divided into 2 groups: Test group (n=30) and Control group (n=30).

Method of data collection: All cases had clinical and laboratory evidence of GDM. Specific questionnaires were prepared and used to collect medical, dietary history and knowledge of the patients on food and glucose levels. Clinical values of HbA1c, Random Blood glucose Levels[11], and Haemoglobin levels were collected prior to intervention and 6 months of post intervention.

Specific Questionnaire was used to collect data (on baseline) through direct interviews by the researcher. Each subject was interviewed with a structured questionnaire. It was used to collect medical, dietary history and knowledge of the patients.

The subjects food intakes were assessed using food frequency questionnaire, while their activities evaluated by

physical activity questionnaire. Anthropometric indices were measured based on standard instructions, and the body mass index was calculated.

Nutritional Status Assessment

Intervention: 30 patients who were included in the study as a test group received conventional nutritional counselling and customised meal plan to achieve adequate protein, Iron, high fibre and complex carbohydrates intake. Monitoring was done during 6months of follow up. The individual meal plan was designed and explained to patient and their families by the following ways.

Educational lecture: Educational lectures were delivered exclusively to the test group. It was presented by the researcher to the GDM Women and their families on the nutritional needs to provide appropriate food with adequate protein, Iron, high fibre and complex carbohydrates to these Women.

Presentation included all the important information required for the GDM subjects. It was concentrated on the elements of the glycemic friendly diet included protein, Iron, high fiber and complex carbohydrates and limiting refined and simple carbohydrates also calorie limitation. Information was provided in a simple way and was explained by pictures for better understanding with the help of info graphics prepared by researcher.

Pamphlets were prepared and distributed to all intervention group participants post the lecture and all the summary information that was presented was found in the sheet which the researcher called it general instruction sheet for GDM subjects. It also includes foods to be included, restricted and to be avoided.

Biochemical parameters

Biochemical data of the participants was obtained from the Clinical Chemistry Laboratory at SVS Medical College.

Blood samples were drawn from the patients prior the nutrition intervention and measured biochemical parameters like haemoglobin, GRBG, (HbA1c) at baseline and 6 months of post intervention period.

Medications

All the participants from both groups (test and control group) took their anti - diabetes medications (Metformin), also receiving iron and folic acid supplementation, Vitamins B, C, D supplements during the study, as recommended by their physicians.

Follow-up

Each patient was monitored during 2 consecutive sessions during the study period (baseline 6 months).

Statistical Analysis

The data thus collected was computerized in a specific program developed on Microsoft Excel 2010 software. The database so prepared was analysed with the help of statistical analysis, t test, p test and the results were transferred to predesigned classified tables, bar diagrams and pie diagrams and are presented as frequencies and percentages for

categorical variables and mean [+ or -] standard deviation (SD) were calculated for all continuous variables. For comparison and differences between means data were analysed using the 't'-test and 'p'-test. A 'p' value of less than (<) 0.05was considered statistically significant.

RESULTS

Demographic characteristics of the study

Sample

The age distribution of subject shows that most of them were in the active age group of 21-25yrs. (Table1, Fig 1)

Most of the subjects were found to be housewives (Table 2, Fig 2)

Regarding food habits, most of them were found to be Non vegetarians (Fig 3) and are having Sedentary Life Style (Fig4)

Most of them belonged to the urban population (Fig 5)

Table No. 1 Age Distribution

Age (Years)	Frequency	Percent
Less than 20	1	3.3
21 - 25	17	56.7
26 - 30	8	26.7
30 & above	4	13.3
Total	30	100.0
Mean ± SD : 26.13 ± 3.59		

Fig No. 1 Age distribution

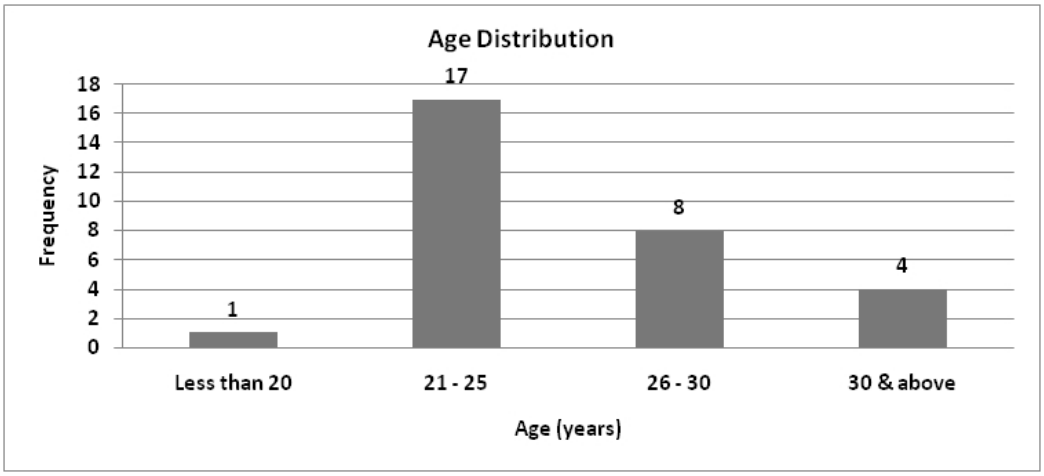


Table No.2 Distribution of Occupation

Occupation	Frequency	Percent
Home maker	22	73.3
Working Women	8	26.7
Total	30	100.0

Fig No.2 Distribution of Occupation

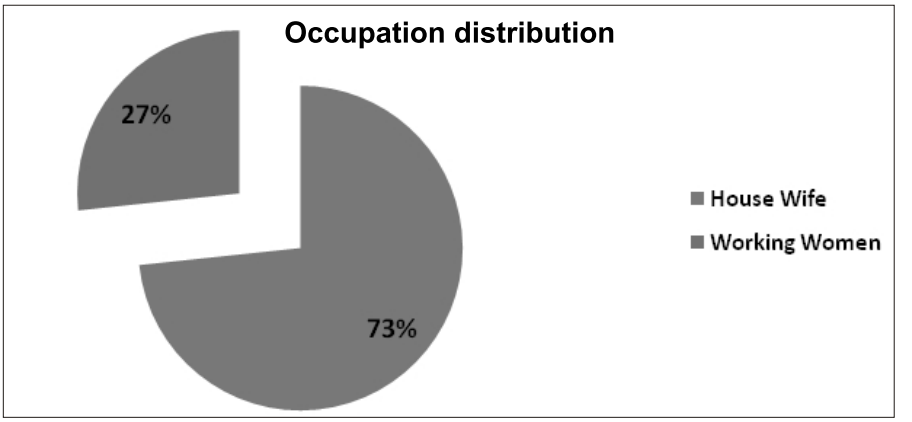
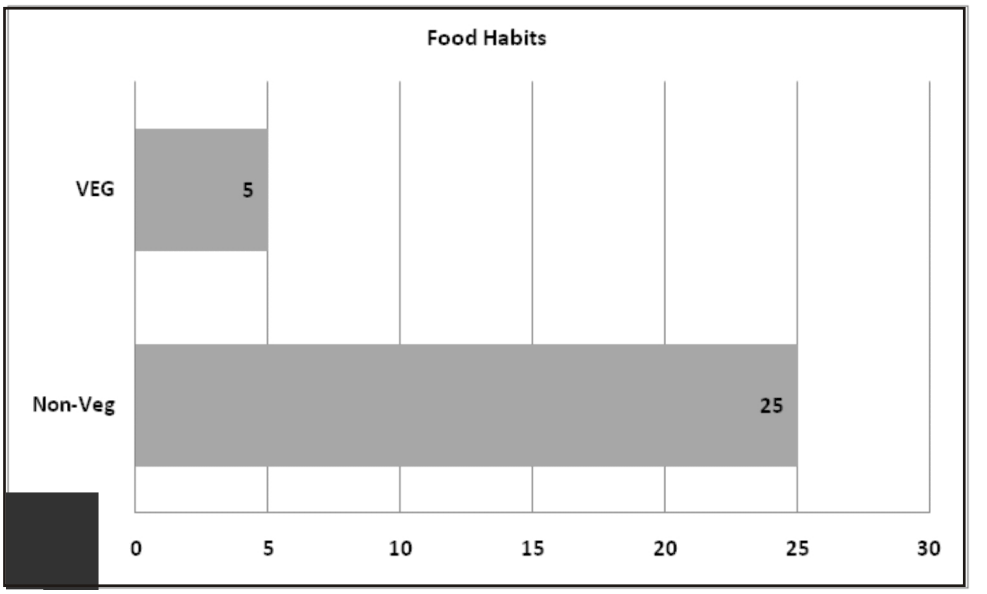
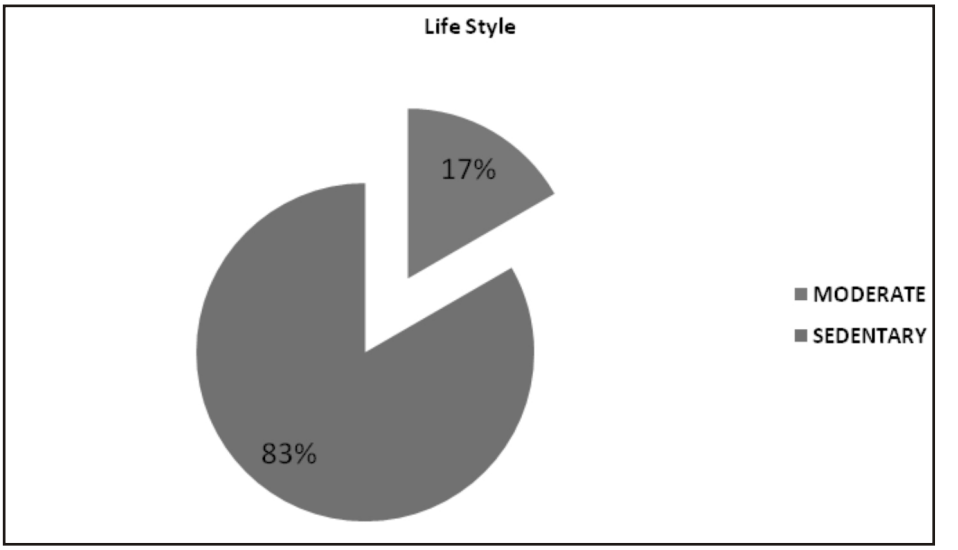


Fig No.3 Food Habits



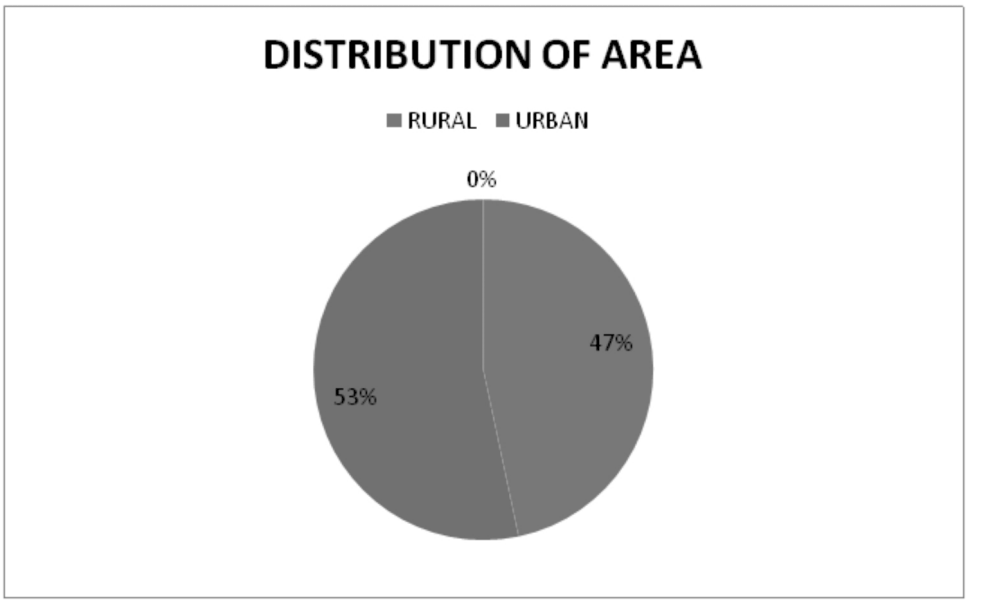
Foot Note: Veg: vegetarian, Non-Veg: Non Vegetarian

Fig No.4 Lifestyle Pattern



Foot Note : Moderate activity, Sedentary activity

Fig No.5 Distribution of Area



Biochemical evaluation of the subjects

This study shows that at baseline, there was no significant difference in the biochemical parameters such as Hemoglobin, (HbA1c), Blood glucose levels between the control and experimental group prior to dietary intervention (P >0.05) whereas the mean value of (HbA1c) in the experimental group in post nutritional intervention was significantly P<0.0001 decreased, represented (7.09±2.34 vs. 5.48±0.61). The other bio chemical parameters also changed significantly in post nutritional intervention. It is clearly noticed that HB levels were significantly increased and blood glucose levels were significantly decreased in experimental group in post Nutrition Intervention (Table 6).

Control Group: Prior and Post Descriptive Statistics Table (Without Nutritional Intervention)

Table No.3. Descriptive Statistics of the study parameters

Parameter	N	Minimum	Maximum	Mean	Std. Deviation
Hemoglobin_prior	30	9	14	11.97	1.362
Hemoglobin_post	30	9	13	11.55	0.953
HbA1c_prior	30	5	8	6.58	0.827
HbA1c_post	30	6	9	7.10	0.993
Glucose level prior	30	167	285	214.77	34.763
Glucose level post	30	200	425	251.00	47.762

Table No.4. The result showing the significance difference between pre and post in clinical parameters

Clinical Parameters For Pre and Post	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)
				Lower	Upper			
Haemoglobin level	0.417	0.607	0.111	0.190	0.644	3.757	29	***0.001**
HbA1c	-0.527	0.456	0.083	-0.697	-0.356	-6.322	29	***0.000**
Glucose level	-36.233	40.383	7.373	-51.313	-21.154	-4.914	29	***0.000**

***p<0.01 is statistically significant**

Experimental Group: Prior and Post Descriptive statistics table (with Nutritional Intervention)

Table No.5. The table showing association between clinical parameters with Nutritional education in pre and post

Parameters	***N***	***Minimum***	***Maximum***	***Mean***	***Std. Deviation***
HB prior Nutritional_Education	30	8.60	14.40	12.7800	1.206
HB_Post_Nutritional_Education	30	11.20	15.30	13.7433	0.769
HbA1c_Prior_Nutritional_Education	30	4.80	8.60	6.3933	1.066
HbA1c_Post_Nutritional_Education	30	4.20	7.00	5.4767	0.617
Glucose_Level_Prior_Nutritional _Education	30	98.00	408.00	186.4667	66.924
Glucose_level_post_Nutritional _Education	30	90.00	180.00	124.4000	22.573

Parameters	Mean	N	Std. Deviation	Std. Error Mean
Haemoglobin level _ prior_Nutritional_Education	12.7800	30	1.20699	0.22037
Haemoglobin level Post_Nutritional_Education _	13.7433	30	0.76909	0.14042
HbA1c_Prior_Nutritional_Education	6.3933	30	1.06607	0.19464
HbA1c_Post_Nutritional_Education	5.4767	30	0.61738	0.11272
Glucose_Level_Prior_Nutritional_Education	186.4667	30	66.92184	12.21820
Glucose_level_post_Nutritional_Education	124.4000	30	22.57341	4.12132

Table No.6 Effect of nutritional intervention program in Experimental Group

Parameter	Prior nutritional **education Mean±SD**	Post nutritional education Mean ±SD	t-value	P-value
Hemoglobin	12.78±1.20	13.74±0.76	6.12	<0.0001**
HbA1c	7.06±2.34	5.48±0.61	4.24	<0.0001**
Glucose values	186.74±66.92	124.40±22.57	5.48	<0.0001**

**** p<0.0001 is highly significant**

Table No.7. Paired Samples Correlations

Paired Samples Correlations			
	N	Correlation	Sig.
HB_With Nutrition Education &HB_Without Nutrition Education	30	0.702	*0.000
HbA1c_With Nutrition Education & HbA1c _Without Nutrition Education	30	0.500	*0.005
Glucose_Level_With Nutrition Education &Glucose_level_Without Nutrition Education	30	0.381	*0.038

***p<0.05 is statistically significant**

Table No. 8. The table showing the Paired Differences between HB, HBA1C Blood glucose Levels with Nutrition Education and without Nutrition Education.

Parameters	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
HB_With Nutrition Education - HB_Without Nutrition Education	-0.96333	0.86323	0.15760	-1.28567	-0.64100	-6.112	29	*0.000
HbA1c_With Nutrition Education - HbA1c_Without Nutrition Education	0.91667	0.92739	0.16932	0.57037	1.26296	5.414	29	*0.000
Glucose_Level_With Nutrition Education- Glucose_level_Without Nutrition Education	62.06667	61.93764	11.30821	38.93877	85.19456	5.489	29	*0.000

Abbreviation: std.= standard, df= difference, Sig.=significant
***p<0.01 is statistically significant**

Discussion: The aim of this study was to review the scientific evidence on nutritional intervention strategies, including diet and physical activity that are effective in reducing the risk of GDM.In the present study, we focused on the roles of dietary patterns on pregnant women with GDM. We found that dietary patterns could alleviate the GDM condition by decreasing the inflammatory condition and affecting the faecal micro biota. The overall dietary pattern can better reflect the impact of food on disease.[12,13] Zareei et al.[14] studied the correlation between dietary status and GDM in 208 pregnant women at 2428 weeks of gestation through a food frequency questionnaire. The results showed that a healthy diet rich in fruits, vegetables, and low-fat dairy products could effectively reduce the risk of GDM. At the same time, other studies[15,16,17] also confirmed that excessive intake of refined cereals, lipids, sugars compared to a small amount of fruits and vegetables prior and during pregnancy will increase the incidence of GDM, suggesting that adverse dietary patterns and lifestyle can affect the production of intestinal flora and inflammatory factors, such as C-reactive protein, thus promoting the rise of fasting blood glucose and abnormal glucose tolerance.

The mean value of HbA1c in the control group (without nutrition intervention) was highly significantly increased post 6 months. The HB levels were significantly decreased and Random blood glucose levels were significantly increased post 6months without nutrition intervention (Table 4).

Whereas the mean value of HbA1c in the Experimental group (with nutritional intervention) was highly significantly $P<0.0001$ decreased than prior nutritional intervention, represented (7.09±2.34 vs 5.48±0.61) where as other bio chemical parameters shows highly significance change post nutritional intervention. It is clearly noticed that HB levels were significantly increased and blood Glucose Levels were significantly decreased post Nutrition Intervention (Table 6). Paired sample correlation for both control (without nutrition intervention) and experimental group (with nutrition intervention) also shows there are significant differences in HbA1c, HB levels and Random blood glucose levels between both groups.

The improved parameters can be explained by the higher intake of Green leafy vegetables, ragi powder[18],fibre, protein, complex carbohydrates, low glycaemic foods and awareness of nutritional knowledge through nutrition intervention. The study showed that proper nutritional counselling by dietician on the intake of diet can result in a better nutritional status.

The roles of dietary pattern management that might alleviate the condition of GDM via affecting the inflammatory condition and intestinal microbiota. Our results provided a new way for the management of GDM.

Conclusion:

The results of this study shows that there is an urgent need for dietary intervention

by diet counselling with nutrition education programs for improving knowledge and skills of GDM subjects towards their condition and dietary management to improve their nutritional status which includes weight recording, diet, exercise and lifestyle changes. Therefore, nutritional counselling by qualified dieticians should be mandatory as part of the medical management to improve the nutritional status of GDM subjects.

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Review Article

EFFICACY OF VITAMIN C IN MANAGING ADVERSE PHYSICAL HEALTH IMPACTS OF TOBACCO SMOKING: A SYSTEMATIC REVIEW.

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Abstract

Introduction: Among all the products of tobacco, cigarette is the most commonly used product in today's world. In 1884, the use of John Bonsack's cigarette making machine made the procedure easy and therefore, the cost of cigarettes was decreased. Tobacco smoking has several deleterious effects on the human body.

Purpose: Tobacco contains many toxic chemicals which are entering in the human body through the lungs system, are responsible for cancer and several non-cancerous disorders, this review paper was carried out to identify how vitamin C works on the inactivation of the harmful chemical components.

Method: This review work has been developed by a systematic review process.

Conclusion: The ill effects of smoking have multiple adverse effects on human life. Vitamin C plays an important role to fight against these problems. This review shows how effectively Vitamin C help in tobacco smoke induced various problems.

KEY WORDS: *Tobacco, Smoking, Nicotine, Toxic chemicals, Cancer, Vitamin C.*

INTRODUCTION

In 15th century, Nicotiana or the plant from which the main ingredient of today's cigarette is collected was believed to have therapeutic usage. It was even used to make toothpaste. But with time, people started smoking, chewing and snoring tobacco. Through research, the deleterious effects of tobacco leaves (when burned) finally observed (2, 4). Nowadays, it has become the biggest problem worldwide because of the addictive, psychoactive substance present in cigarette smoke which affects our body through psychopharmacologic mechanism. Some gaseous components, some liquid volatile components, certain tobacco-specific nitrosamines, solid particles, etc are the main components found in

cigarette smoke(8, 11).While burning a cigarette, the smoke emitted contains about 4000 harmful chemicals responsible for so many cancer and non-cancerous disorders like heart disease, stroke, lung disease, diabetes, chronic obstructive pulmonary disease, etc (3, 12, 19). To control and save chronic smokers from the harmful effects of cigarette smoke, Nicotine Replacement Therapy has been developed along with counselling (3,18). Vitamin C, commonly found in fruits and vegetables is an antioxidant, helps in diseases cause due to cigarette smoking by inactivating the harmful chemical components. According to research, for adults 30mg/kg body weight/day of vitamin C is helpful to prevent so many diseases and problems related to the harmful effects of commercial cigarette smoke (5, 7,9, 15, 16, 18). This study is designed to help chronic smokers to fight against the consequences of tobacco smoke. It is difficult to detach chronic cigarette smokers from cigarette. Therefore, an alternative way is needed through which at least the problems they face can be reduced Costs.

REVIEW OF LITERATURE

Invention Of Tobacco

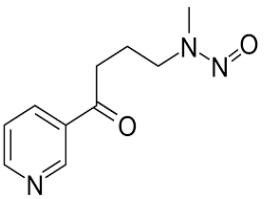
Tobacco, the main ingredient of cigarette has been used for hundreds of years, mostly smoked, but sometimes chewed or snorted. Tobacco have previously been found to be used in religious ceremony and also as a medicine by the native population of America to treat medical conditions like ulcerated abscesses, fistulas, inveterate polyps, cold, catarrh, diseases of glands, etc. It was also used in anaesthesia. Even, it was used to make toothpaste combining with lime or chalk. In 15th century it was believed that each and every herb has some therapeutic uses and nicotiana was not an exception. Even nicotiana was called the 'God's remedy' and also 'Holy Herb'. Later, it's use in different country both in the form of reeds and smoking tube started increasing. Among the 60 species of nicotiana, *Nicotianatabacus* and *Nicotianarustica* are mainly used commercially till now. Among all the products of tobacco, cigarette is the most commonly used product in today's world. Previously the cigarette produced were different from today's cigarette. A blend was prepared using oriental tobacco, sugar and additives to produce a cigarette. In 1870 cigarette was not so popular compared to today's world. Because the production procedure of cigarette was time consuming as it was hand rolled. In 1884, the use of John Bonsack's cigarette making machine made the procedure easer and therefore, the costs of cigarette were also decreased(2, 4).

Chemical Composition of cigarette

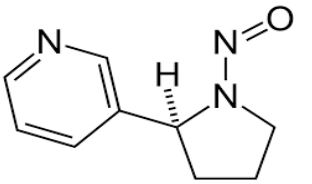
Mainly Cigarette smoke contains gaseous components; such as carbon monoxide (CO), hydrogen cyanide (HCN), and nitrogen oxides. The liquid volatile components found in the vapour phase of smoke are tobacco alkaloids, formaldehyde, acrolein, benzene, and certain N-nitrosamines. Nicotine, phenol, poly cyclic aromatic hydrocarbons (PAHs), and certain

tobacco-specific nitrosamines (TSNAs), acrolein, 1,3-butadiene, benzene, benzo pyrene, **NNN**, **S-NAB** and **NNK** are contained in the submicron-sized solid particles that are

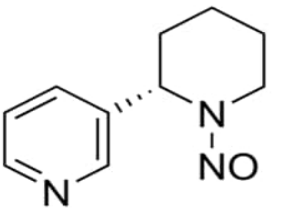
Psychopharmacologic Mechanism of Cigarette Smoking



NNK (4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanone**)**



NNN (N-nitrosonornicotine)



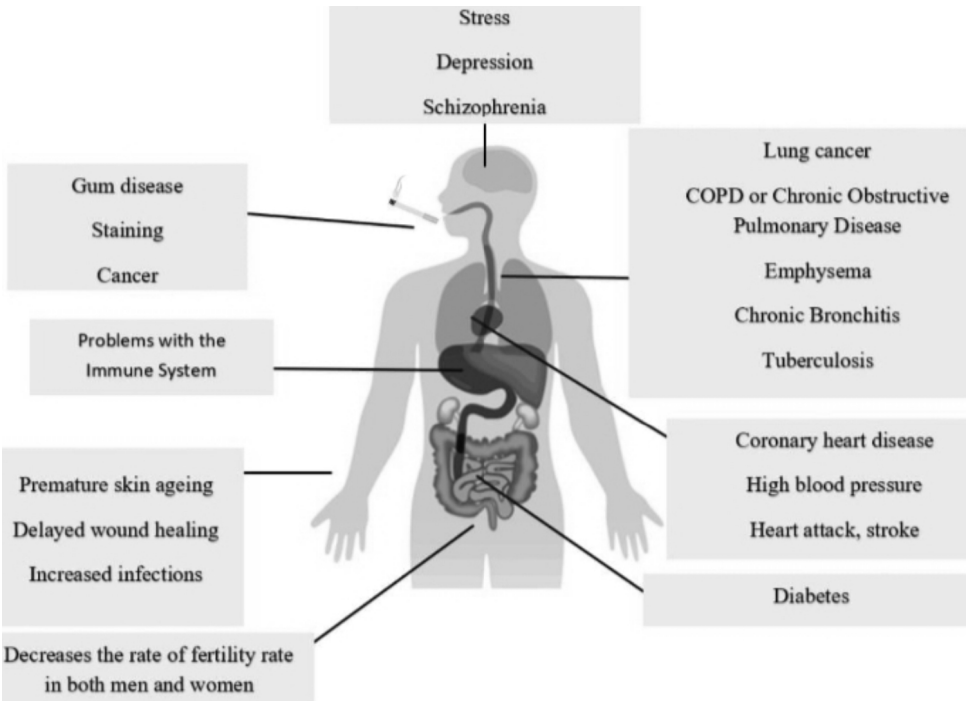
S- NAB ((S)-N-Nitrosoanabasine

The addiction of nicotine during cigarette smoking cause effects in human body via psychopharmacologic mechanism. Nicotine activates Brain's mesolimbic dopaminergic reward system and produces physical and neurobiological withdrawal symptoms. Nicotine acts as an agonist for neuronal nicotinic acetylcholine receptors (**nAChR**s)-pentameric ionotropic (Na^+ and Ca^{2+}) receptors found presynaptically throughout the central nervous system (CNS) and postsynaptically in the autonomic nervous system that modulate the release of neurotransmitters and ganglionic potentials. After chronic nicotine treatment, nAChR numbers are increased, which is associated with the development of behavioural tolerance to nicotine in animal models. Nicotine also acts as an antagonist, as it can reduce the **nAChR** turnover and accumulation of nAChR at the cell surface. Measured nicotine levels in the arterial and venous circulation indicate that individual smokers can obtain plasma nicotine levels of 2050 ng/ml. This concentration range (≈100300 nm) is one order of magnitude less than the equilibrium binding and activation concentration of l-nicotine to the a4b2 receptor, the predominant nAChR in the brain, but is nearly equal to the effective concentration for inactivation and accumulation of the a4b2 receptor (8, 11).

Adverse Effects of Tobacco Smoking on Human Systems

Tobacco smoking has a several harmful effects on the human body. Tobacco contains many carcinogenic and toxic chemicals that are entering in the human body through the lungs route. These toxic effects are responsible for cancer and also several non-cancerous disorders, like heart disease, stroke, lung diseases, diabetes, and Chronic Obstructive Pulmonary Disease (COPD), including emphysema and chronic bronchitis. Smoking also increases the risk for tuberculosis, certain eye diseases and problems with the immune system, such as rheumatoid arthritis. It also decreases the fertility rate and susceptibility to

sexually transmitted diseases. Smoking decreases the rate of fertility in both men and women. Tobacco smoking has a huge impact on mental health. It is commonly found that smokers believe cigarettes can treat their mental health but unfortunately there is an increase in several health problems. The bad effects (such as stress, Depression, and Schizophrenia) of smoking on mental health depends on the frequency of smoking (12, 19).



Effects of Tobacco Smoking

Management of ill effects of tobacco smoking

The pharmacological effects of nicotine are the main reason behind the tobacco smoking addiction. It has become important to take some necessary steps to manage the ill effects of cigarette smoking induced problems, because now one in every four men is proved to be the daily smoker in this world.

Nicotine Replacement Therapy

Nicotine Replacement Therapy (NRT) is an initiative taken to reduce the motivation to consume tobacco through which it has become possible to protect ourselves from the harmful effects of nicotine and its addiction. There are so many forms of NRT products used such

as nasal spray, oral inhaler, gum, transdermal patch, nicotine lozenge, and even in the form of tablets. Along with these products E-cigarette or electronic nicotine delivery system (ENDs) have also been introduced for better result and the acceptance rate of E-cigarette is better due to its look, feel and taste. Another new approach is nicotine vaccines to treat nicotine dependence. But the use of these products and systems or vaccines are believed to be more effective when counselling is done along with these to quit smoking. It is difficult to quite the addiction of cigarettes permanently and the smoke emitted from a burning cigarette contains about 4000 harmful chemical components. Therefore, a special attention is given in the identification of disease-causing chemicals and its inactivation (3, 18).

Vitamin C - A Panacea for everyone

Vitamin C, also known as ascorbic acid or hexuronic acid or antiscorbutic acid is water soluble, colourless, odourless crystalline micronutrient required for multiple biological function, which is found in citrus and other fruits and vegetables. Vitamin C is an essential component in the prevention of diseases and is good at acting as an antioxidant. Due to the absence of gluconolactone-oxidase in human body, except the humans most of the mammals are able to synthesis vitamin C from glucose, due to the absence of gluconolactone-oxidase in human body, therefore extra vitamin C is needed to be consumed by humans from foods. Along with the electron donating property, vitamin C also helps in tissue repairing, in cardiovascular diseases, in

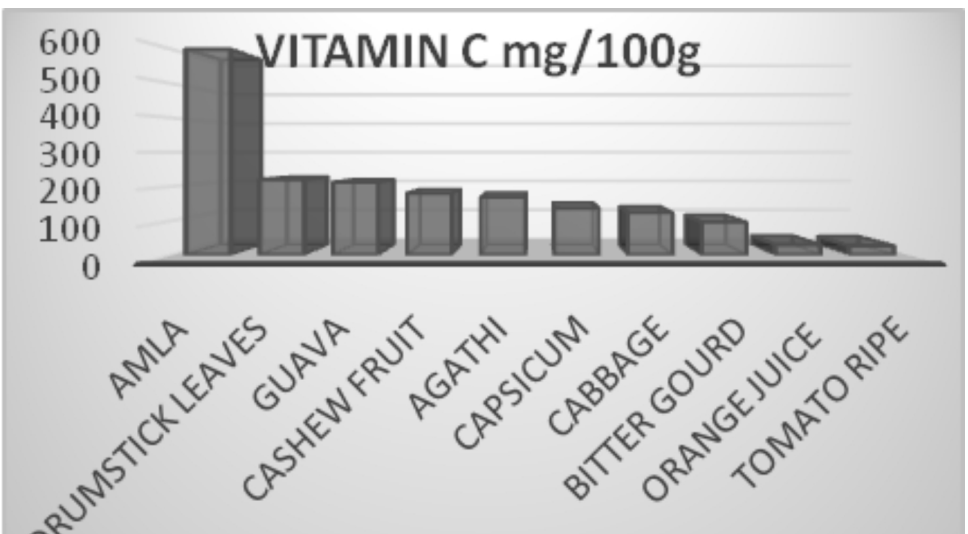


Fig 2 (Graphical representation of Vit-C content of some fruits and vegetables)

synthesis of the hormones like noradrenalin/ adrenaline and peptide hormones, gene transcription, regulates the translation, helps in collagen formation, immunologic functions, drug detoxification, carnitine synthesis, cellular respiration, tryptophan metabolism, prevention of cataract, cholesterol metabolism, iron absorption and many more. Even, according to the studies, vitamin C supplementation is proved to be effective in healing, infections, tissue damage, coronary heart disease and so on. Some good sources of vitamin C are amla, guava, orange, lime, green leafy vegetables, and mainly most of the fresh fruits and vegetables but it is absent in animal sources(15).

From scurvy to cancer, the impact of vitamin C supplementation on disease prevention have already been proved. The high doses of vitamin C when given intravenously, increases the hydrogen peroxide dose-dependently and the elevated levels of hydrogen peroxide may be the reason of anti-cancerous effect of vitamin C. Not only that, there are so many signs which prove its anti-cancerous effect (5, 15).

Role of Vitamin C in management of adverse effect of Tobacco Smoking

Vitamin C plays an important role as antioxidant along with giving protection against oxidative stress-induced cellular damage by scavenging of ROS (Reactive Oxygen Species). Vitamin C is a powerful reducing agent and a scavenger of free radicals, shows a very potent scavenging activity against oxygen and nitrogen oxides species like superoxide radicals, hydroxide radicals, hydrogen peroxide, etc. Some studies show that smoking has decreased the amount of vitamin C in humans, which is increased oxidative damage in the smoker's body. Vitamin C effectively protect lipids in human plasma against peroxidative damage by scavenging oxygen-derived free radicals (7, 9, 15).

According to research, the maternal smoking during pregnancy (MSDP) can affect the organs of the child (for example it can affect multiple organs like lung, brain and even vasculature). Along with deficits in pulmonary functions, asthma, wheeze may also increase. It is proved that vitamin C supplementation during pregnancy can be beneficial to fight against the adverse effects of MSDP. MSDP also bring changes in DNA methylation of the child too in cord blood, placenta and even in buccal epithelium. In some new findings, it is stated how efficiently vitamin C supplementation to the expectant mothers normalized the changes in DNA methylation (13, 14).

Not only that, researches about the memory impairment induced by Waterpipe Tobacco Smoking (WTS) and the impact of vitamin C on this problem proved that memory impairment which is linked to waterpipe tobacco smoking associated with oxidative stress is a big problem that can be improved by using vitamin C. Vitamin C is also effective against the memory impairment related to different types of diseases. It is now clear that due to cigarette smoke,

oxidative stress increases significantly. In a study, the effect of antioxidative enzyme expression was tested and the result was actually positive. According to the result, how the gene expression is getting influenced due to the intake of ascorbic acid was proved(1,17).

Research says, a commercial cigarette produces about 100-200 µg p-benzosemiquinone while burning which gets converted into p-benzoquinone(p-BQ) later, the causative factor of the diseases like emphysema (Pathophysiological feature of COPD), Carcinoma In Situ (CIS), CVD, Myelodysplastic Syndrome (MSD), and even it affects our eyes too. In our body p-BQ affects our lungs and gradually spreads to the blood and to multiple organs. A dose of 30mg/kg body weight/day of vitamin C have shown its efficiency to prevent accumulation of p-BQ. This dose of vitamin C have also played important role in prevention of CVD, Myelodysplastic Syndrome (MDS) and even the Carcinoma In Situ (CIS). But apart from there are so many things to be explored, along with the known result there are unknown results too which is waiting to be proved in this field which proves how effective vitamin C is for the smokers(3).

CONCLUSION

Tobacco smoking increases the toxic substances in the body and mostly have lower concentration of vitamin C, which results in many dangerous risk factors like cancer and many non-cancerous diseases. But Vitamin C can defend our body from the deleterious effects of toxic chemicals and neutralize these toxins before they do any harmful damages. Vitamin C protect lipids in human plasma against peroxidative damage which occurs due to the scavenging of oxygen-derived free radicals. Vitamin C is a powerful antioxidant that helps to prevent the damage caused by free radicals. Thus, according to many studies, it can be concluded that incorporation of vitamin C in adequate quantity is an effective way to reduce the negative impacts of smoking on our physiological systems.

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Original Research Article

OBSERVATIONAL STUDY ON INITIATION OF NUTRITION IN CRITICAL CARE NON-SURGICAL PATIENTS IN A PRIVATE HOSPITAL SETTING.

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ABSTRACT

Objective: The majority of critically ill patients are malnourished due to their high catabolic state which leads to increased healthcare-related expenses and a negative impact on patient outcomes. This study aims to assess the compliance of medical nutritional management followed in the hospital with ESPEN guidelines for non-surgical critically ill patients in relation to the time of initiation of nutrition, time to achieve target energy-protein goals, and reasons associated with delay in providing nutrition.

Methods: Prospective observational study with 120 non-surgical patients, age >18 years, hospitalised in the intensive care unit, evaluated according to ESPEN guidelines for critically ill patients. Upon admission, a nutritional assessment was done of the patient to find out the nutritional requirements. The primary endpoint was the time taken to initiate nutrition and the secondary endpoints were time to achieve full feeds and reasons for the delay in the initiation or achieving recommended total energy and protein requirement.

Results: In 78.3% of the samples, nutrition was initiated within 48 hours after ICU admission. The average time to initiate nutrition was approximately 29 hours. On follow-up after 3 days, 24.2% of patients received insufficient nutrition. The median time taken to reach recommended nutritional requirement was 72 hours.

Discussion: The ESPEN guidelines state that patients who are hemodynamically stable and have a functioning GT should start receiving nutrition within 24 to 48 hours after being admitted to the ICU. The median duration to start nutrition in our study was 29 hours which was well within the recommended range for 78.3% of the patient. Comparable to earlier studies of a similar nature where the percentage of patients with early initiation ranged from 33.3% to 80%, thus the results of this study support those previously conducted internationally describing nutritional adequacy in the critically ill.

INTRODUCTION

A critically ill patient is a patient who has a life-threatening illness and often involves multisystem dysfunction which can increase the risk of morbidity and mortality (Mahmoud & Yearwood, 2019). They experience severe cardiovascular, neurological or pulmonary problems, frequently occurring in combination. Rapid catabolism of skeletal or lean mass necessitates critical care as the net negative nitrogen balance leads to muscle atrophy (Csg & Fand, 2020). Muscle wasting occurs at a rate of 2% to 3% each day in critically ill patients and is most severe in the initial few days of illness (Flower & Puthucheary, 2020).

According to ESPEN guidelines (2019), all critically ill patients admitted should be considered for medical nutrition therapy as an accepted standard of care especially if their anticipated length of stay in the ICU exceeds 48 hours. Critical illness raises resting energy expenditure while inadequate administration of nutrition encourages malnutrition. In 1970, Cuthbertson had first characterised the response to critical illness as the 'ebb' and 'flow' phases. The 'ebb' phase comprises the acute early phase of hemodynamic instability related to a decrease in cardiac output and body temperature followed by the 'flow' phase including a period of increased energy expenditure and catabolism which can last up to 48 hours and a later period of anabolism for the following 5 to 7 days (Sharma et al, 2019; Cuthbertson, 1970). ICU patients stand at risk of developing malnutrition due to their high catabolic state and need to be fed accordingly.

A severe previous loss of appetite, muscle atrophy, and multiple comorbidities prior to admission also puts the patient at nutritional risk. A study by Hejazi et al (2016) found that 29% of critically ill patients were malnourished upon admission. Another study reported 37% of critically ill patients as either moderately and severely malnourished on admission (Sungurtekin et al., 2008). In a systematic review recently done, the presence of malnutrition ranged from 38% to 78% in ICU patients (Lew et al., 2017). Among adult patients, nutritional risk at admission was significantly correlated with increased length of hospital stay (Caccialanza et al., 2010). Longer length of stay of patients was also influenced by worsening of nutritional status during their hospital stay. The decline in nutritional status in ICU was shown to be caused by the delay in the commencement of nutrition and inadequate feeding which increased the incidence of malnourished patients from 28% on admission to 58% malnourished patients on ICU discharge day (Hejazi et al., 2016). Careful planning and prompt nutrition therapy implementation are crucial to prevent

deterioration of the health of the patient.

The ESPEN guidelines recommend 20-25 kcal/kg body weight/day energy in the acute and early phase patients of critical illness which increases to 25-30 kcal/kg body weight/day in the anabolic-phase or severely malnourished patients (Kreymann et al., 2006). Protein should be provided progressively to attain about 1.3 g/kg of body weight protein per day during critical illness (Singer et al., 2019).

For patients in need of critical care, an oral diet is to be favoured over any other nutritional support therapy. Orally, if the patient can meet more than 70% of his demands from days three to seven, without risks of vomiting or aspiration was deemed appropriate. Provided oral intake is contraindicated, early enteral nutritional support should begin within 24 to 48 hours of ICU admission if the patient's hemodynamically stable and digestive system is intact. Enteral nutrition is preferable to parenteral nutrition due to more physiologic absorption and utilization of nutrients in EN and it also preserves the integrity of the gut's mucosal structure and barrier function. Parenteral nutrition should be implemented within three to seven days only if both oral and EN are contraindicated (Singer et al, 2019).

Prompt administration of adequate nutrition to the patient can reduce disease severity, complications, and length of ICU stay; improve the patient's treatment outcome, and minimize costs. Similar results were seen in a study done by Yu et al (2021), where enteral nutrition was initiated within 48 hours after admission to the ICU showed significantly higher levels of serum albumin and prealbumin levels in the patients. Additionally, both the time spent in ICU and ventilator time were significantly shorter.

In research by Osooli et al (2019), enteral nutrition was started after 48 hours in 28.6% of patients which delayed achieving complete caloric requirements on time. Overall, malnutrition set in for 84% of the study population as a result of failing to meet a minimum 80% of protein and energy target during follow-up which increased mortality rates, risk of infection, and length of stay.

Once the timing and the route of nutrition have been decided, the dose of nutrition should also be taken into account. To prevent overnutrition, the energy/protein goal should be attained gradually and not earlier than the first 48 hours. Progression should not be overly abrupt or have too rapid increases. In the acute phase of illness, hypocaloric nutrition (not exceeding 70% of energy expenditure) should be delivered and after day 3, caloric delivery can be increased up to 80 to 100% of the measured energy requirement (Singer et al., 2019). For the first 72 hours of a critical illness, actual energy expenditure shouldn't be the target since early full feeding leads

to overfeeding as it adds to the endogenous energy production which already amounts to 500-1400 kcal/day. Early full feeding also raises the risk of refeeding leading to electrolyte imbalance post beginning of nutritional support (Mcknight et al, 2019). The imbalances may lead to heart, lung, or gastrointestinal-related complications. A careful and gradual re-introduction of nutrition will aid in reducing the risk of refeeding syndrome, especially for extremely malnourished patients or those who were starving before admission. On the other hand, an intake that is excessively low - below 50% - can result in severe calorie deficit, exhaust the body's energy stores, loss of lean body mass and exacerbate infection problems. Late initiation, enteral feeding intolerances, and interruptions are the main reason for under nutrition (Simene et al., 2020). The dose of nutrition and its increment should be done carefully.

Enteral nutrition is contraindicated in case of uncontrolled shock and hemodynamic instability, uncontrolled life-threatening hypoxemia, hypercapnia, or acidosis. However, low dose EN can be begin as soon as the shock is controlled. Another result of delayed delivery of nutrition could be active upper GI bleeding, in such a case nutrition only to be initiated when the bleeding has stopped and no signs of re-bleeding are observed. Other causes include overt bowel ischemia; in patients with high-output intestinal fistula if reliable feeding access distal to the fistula is not achievable; in patients with abdominal compartment syndrome; and gastric aspirate volume greater than 500 ml/6 hr lead to delay in EN. (Singer et al., 2019).

Gastrointestinal tract complications (e.g., GI bleeding) and hemodynamic instability were found to be the most common reasons for the late initiation of enteral nutrition (Pasinato et al., 2016).
Time, dosage, and route of nutrition all are very important factors to deliver the best possible outcome in critically ill patients. It should not be considered separate but rather altogether as one entity should be taken into consideration.

METHODOLOGY:

Purpose:

This study was carried out to assess the current state of nutrition delivery for the critically ill in a private hospital setting in India in comparison to international standards (ESPEN). The findings of this study can be used to identify barriers to timely receipt of nutrition and develop strategies to reduce the time for delay in initiation of nutrition and delay in energy and protein delivered to recommended amounts.

Study design and Population:

An observational prospective study was conducted in the ICU of a private hospital

in Delhi, India to see adherence to ESPEN guidelines. Patients above 18 years of age, both males and females, non-surgical, requiring critical care, and expected to stay at least 48 hours in the ICU were included in the study. Patients who are deceased before initiation of any nutrition were excluded from the study. Convenience sampling was used meaning that as the patients were admitted to ICUs, their data was collected considering they met the inclusion criteria. A comprehensive systematic review of the literature was conducted on nutrition therapy for the critically ill. Based on the current state of the evidence, indicators to be collected for data analysis were selected and data collection was completed.

Sample Size Calculation:

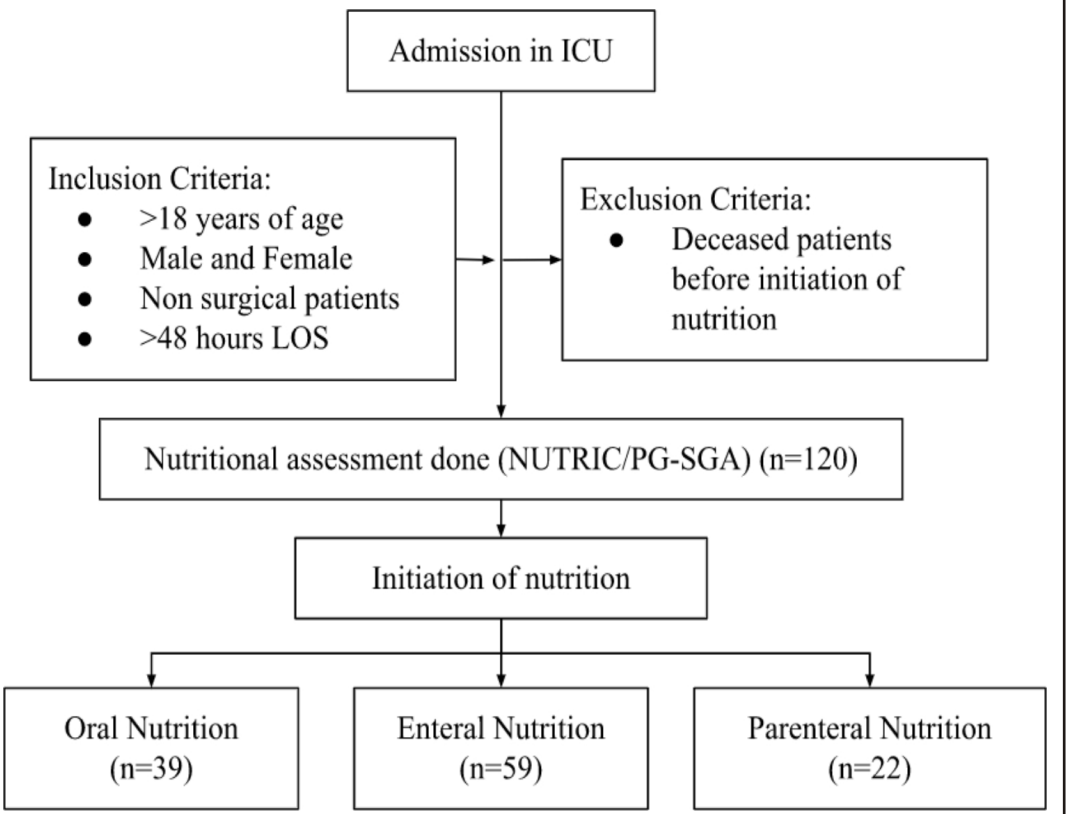
The sample size calculation was done based on the percentage of patients where nutrition was initiated within 48 hours post ICU admission. In an article by Osooli et al (2019), this was reported as 71.4% (π =0.714) of the study population. To estimate this within a margin of error of 10% (L=0.10) on either side, the sample size came to a minimum of 79 as per the following formula:

$$n \geq \frac{z^2_{1-\alpha/2}\,\pi(1-\pi)}{L^2}$$

Data collection:

Upon admission of the patient to the ICU, a nutritional assessment using PG-SGA/NUTRIC was conducted to determine the nutritional requirement of the patients followed by confirmation of inclusion and exclusion criteria (Figure 1). Baseline data collection measures included demographic data such as age and sex. The patient's data including the primary diagnosis, comorbidities, time of admission to ICU, and nutritional assessment score was collected using the Computerised Patient Record System (CPRS). Length of time, route, and dose of nutrition on initiation was also recorded. Percent of goal energy and protein delivered after day three of initiation of nutrition was collected through the critical care flow sheet in ICU and compared to the recommended amount during the initial nutrition assessment. The ESPEN recommendations clearly state that after day 3, nutrition administration can be increased up to 80-100%, hence post the third day was chosen for evaluation (Singer et al., 2019). The patients were then individually observed until reaching recommended calorie- protein requirement, discontinuation of nutritional support, discharged from ICU or death.

The primary endpoint was the time taken to initiate nutrition and the secondary endpoints were time to meet complete nutritional requirement and reasons for the delay in the initiation or achieving recommended total energy requirement.



Statistical analysis:
Statistical analyses were performed using Microsoft Excel (2019 edition). All the data was entered and descriptive analysis was performed. Continuous variables with a normal distribution were summarised using means and standard deviations. Continuous variables with a non-normal distribution were described using medians. Percentages (frequency) were used to describe the distribution of categorical variables.

RESULTS:
A total of 120 patients who fulfilled inclusion criteria were included in the study. The analysis and interpretation of data collected which were classified, tabulated, and analysed based on the objectives of the study and is presented below.

Demographic data:
The research included 57.5% male (n=69) patients and 42.5 % (n=51) as female patients as shown in Table 1. The mean age was 64.27 ± 16.73 years. 64.2% of patients (n=77) were identified to be at nutritional risk based on nutritional assessment (NUTRIC score ≥5 and PG- SGA ≥7).

Table 1: Characteristics of patients admitted to the intensive care unit

Characteristics	**Total (N = 120)**
Age mean (SD), years	64.27 ± 16.73
Sex, n (%) Male Female	 69 (57.5) 51 (42.5)
PG-SGA Score <7 *Score ≥7* *NUTRIC* *Score <5* *Score ≥5*	 33 (27.5) 44 (36.67) 10 (8.33) 33 (27.5)

Medical nutrition therapy:

In the intensive care unit, it was noticed that nutrition was initiated early (within 48 hours) in 78.3 % (n=94) patients while for 21.6% (n=26), initiation of nutrition was delayed (Figure 1). Time taken to initiate nutrition therapy was approximately 29 hours (Table 2).In 49% (n=59) of patient the mode of nutrition was enteral followed by oral in 32% (n=39) and parenteral nutrition in 18% (n=22).

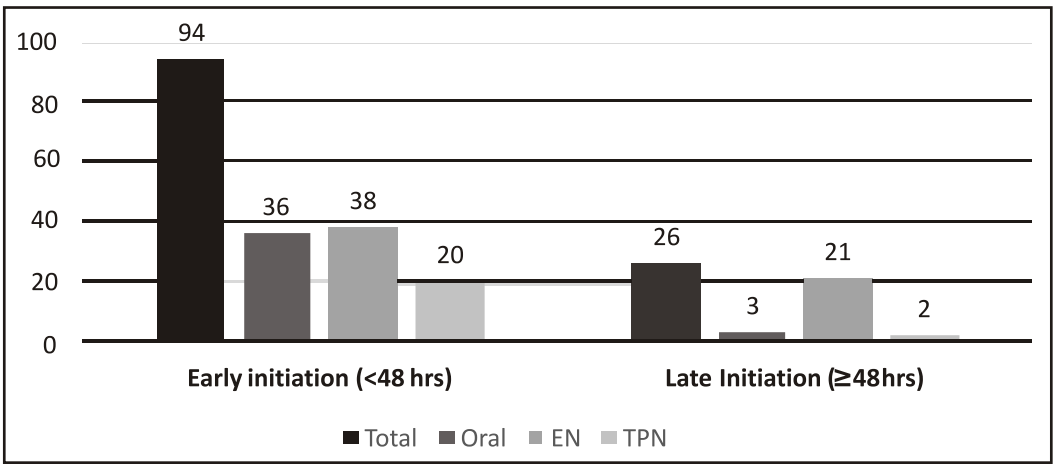


Figure 2: Chart representing data on early and late initiation based on different route of nutrition

Table 2: Characteristics of supply of nutrition to critically ill patients

Variables	**N (%) [n=120]**
Nutrition started within 48 hours Nutrition did not start within 48 hours	94 (78.33) 26 (21.67)
Route of Nutrition Oral • Initiated Early • Initiated Late Enteral Nutrition • Initiated Early • Initiated Late Parenteral Nutrition • Initiated Early • Initiated Late	 39 (32.50) 36 3 59 (49.17) 38 21 22 (18.33) 20 2
Time taken for initiation of nutrition, Median (hours)	29.09
Reached 80-100% EE after day 3 Oral EN PN	91 (75.83) 39 38 14
Time taken to reach recommended EE(energy expenditure) Median (hours)	72

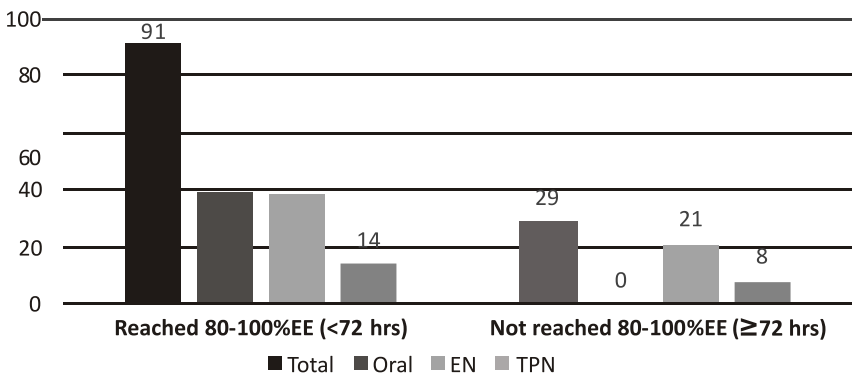


Figure 2: Patients who reached their target Energy Intake within 3 days

Post 72 hours, 76% (n=91) reached minimum 80% of energy target while 24.17% (n=29) of patients received insufficient nutrition (< 80% EE). All the patients who were started on oral intake attained their target energy during routine rounds after 3 days.(Figure 2). The median time taken to reach recommended energy requirement was 72 hours (Table 2).

Table 3: Reasons for delayed nutrition and insufficient nutrition during follow up

Variables	**N (%) [n=120]**
Reasons for delayed initiation	
Hemodynamic instability/Shock	18 (69.23)
Procedure/Investigations	11 (42.31)
High gastric residual volume	2 (7.69)
Gastrointestinal bleeding	3 (11.54)
Aspiration	3 (11.54)
Vomiting	2 (7.69)
Reasons not reached 80-100% EE	
Procedure/Investigations	19 (65.52)
Electrolyte optimization through free water (hypernatremia)	5 (17.24)
Hemodynamic instability	4 (13.79)
Aspiration	5 (17.24)
GI Bleed	2 (6.90)
Fluid restriction	4 (13.79)
Dysphagia	4 (13.79)
Diarrhoea	2 (6.90)

DISCUSSION:

According to the ESPEN guidelines, patients who are hemodynamically stable and have a functioning GT should receive nutrition, within 24 to 48 hours of ICU admission. In our study, the median time to initiate nutrition was 29 hours which was well within the range as per the recommendations in 78.3% of the patients. Comparable to other similar studies done before (Salciute-Siemene et al., 2020; Osooli et al., 2019; Kozeniecki et al., 2015; Stewart el al., 2016) percentage of patients with early initiation ranged from 33.3% to 80%. The findings of this study confirm those

previously conducted internationally describing nutritional adequacy in the critically ill. The most common reasons for the delay in nutrition were hemodynamic instability (69.23%) and procedure (42.23%) such as intubation, tracheostomy, etc. Other reasons were found to be gastrointestinal complications (30.77%) such as high gastric residual volume, GI bleeding, and aspiration (7.69%).

According to the ESPEN guidelines, the first preference was given to use the gut either orally or through enteral support. Thus, in case of no contraindications, oral intake was encouraged, and it was noticed that second priority was given to EN. Enteral nutrition refers to the provision of nutrients through the gastrointestinal tract to maintain the body's metabolism. The gastrointestinal tract plays an important role in immune defense. Compared with parenteral nutrition, enteral nutrition helps in maintaining the integrity of the intestinal mucosal structure and barrier function. Thus, for the 49.5% (n=59) patients who can't be fed orally, EN was initiated.

Overall, the delivery of nutrition was gradual and progressive in nature. The same can be seen for enteral feeding which was majorly initiated on a low dose of 25 ml per hour for 88.13% (n=59) of patients and gradually increased to full feed over a span of a few days. This complied with the ESPEN guidelines that advise starting on a low dose first to prevent overfeeding and refeeding syndrome and gradually the nutrition can be increased up to 80%. The median time taken to reach recommended energy requirement came out to be 72 hours which is found to be in compliance with ESPEN guidelines to receive at least 80% of the target energy by day 3. However, one-fourth (24.17%, n=29) of the patients failed to reach their energy target by day 3. For 65.5% of the cases, insufficient nutrition was attributed to the fact that the nutrition was interrupted or withheld for the preparation for extubation or some other procedure/investigation. It was also seen that delivery/dosage of nutrition was not increased in some cases which lead to insufficient nutrition intake. The primary reason was clinical instability due to shock or hemodynamically unstable patients with high support on NORAD (13.79%). Sometimes, it was due to electrolyte imbalance (17.23%) i.e., hypernatremia for which the patient was restricted in terms of volume of feed.

LIMITATIONS:

This was a small, single-center study limiting external validity. Large multicenter studies are needed to further validate the findings. This was a quality improvement research to determine compliance to ESPEN guidelines and its barriers. Thus, outcomes were not measured and therefore cannot comment on implications of sub-optimal provision of nutrition.

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CONFLICT OF INTEREST:

The authors declare no conflicts of interest.

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Original Article

ROLE OF GUT MICROBIOTA IN THE DEVELOPMENT OF INSULIN RESISTANCE AMONG PCOD PATIENTS.

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Abstract

Polycystic ovarian syndrome (PCOS) is a complex endocrine and metabolic disorder characterized by hirsutism, hyperandrogenism, ovulatory disorders, menstrual disorders, and infertility. Though its etiology remains unclear, insulin resistance (IR) is believed to be the major pathologic basis for reproductive dysfunction. Hyperinsulinemia or insulin resistance/hyperinsulinemia is associated with chronic inflammation, hormonal changes, follicle dysplasia, altered endometrial receptivity, and miscarriage or infertility. It also increases the incidence of complications during pregnancy and complications related to anxiety, depression, and other mental disorders. Gut microbiota, a 'second genome' acquired from the human body, can promote metabolism and immune responses through interactions with the external environment. Aberrant gut microbiota can lead to insulin resistance, which is closely associated with the development of PCOS. Gut microbiota play an important role in PCOS and T2DM. Management for this with probiotics, prebiotics and synbiotics may be suggested as new treatment options for his PCOS. The aim of this review is to describe the relationship between PCOS and the gut microbiota along with possible mechanisms and to understand new therapeutic approaches that can be developed.

Keywords: PCOS; dysbiosis; gut microbiota; insulin resistance.

Introduction:

Polycystic ovary syndrome (PCOS) is one of the most common yet most neglected gynecological endocrine disorders widely believed to be the leading cause of infertility thereby affecting 8-13% of women of childbearing age worldwide. PCOS is characterized as hyperandrogenism along with ovulatory dysfunction and polycystic ovarian morphology (PCOM) which means excessive production of androgen hormone by the ovaries. This continuous condition leads to irregular menstrual cycle, numerous cysts that leads to infertility among them. This syndrome is characterized with many gynecologic, dermatologic, metabolic and psychologic abnormalities such as depression, anxiety, sexual dysfunction and social

problems specially affecting her identity and quality of life. This continuous increase of incidence of PCOS attributes to insulin resistance (IR) amalgamating with glucose intolerance, type 2 diabetes (T2DM), dyslipidemia, obesity and even cardiovascular disease. [1][4]

The microbiota community is acknowledged as a complex ecosystem of microorganisms including bacteria, viruses, protozoa and fungi. These communities exist in almost all the districts of the human body including gastro-enteric tract (gut microbiota), skin (skin flora), mouth (oral flora), respiratory system (respiratory tract microbiota), and the vagina (vaginal microbiota) where each plays vital role in regulation of homeostasis via different kind of pathways in numerous systems. The gut microbiota is the most abundant and functionally important microbiota, containing approximately 1014 resident microbes and commensals in the human gut. Many studies have shown close correlation between the gut microbiota and human metabolic levels. The development and pathogenesis of various endocrine and metabolic diseases are influenced by the structural dynamics of the intestinal flora. Tremelene et al. proposed a hypothesis called DOGMA (dysentery) which includes a possible sequence of events in the pathogenesis of PCOS- disrupting the microflora, connections between intestinal epithelial cells and increases the permeability of the intestinal mucosa, Leaky gut causing leakage of lipopolysaccharide (LPS) into the systemic circulation, and the resulting activation of the immune system can impair insulin receptor function and cause Insulin Resistance. Insulin Resistance /hyperinsulinemia can enhance testosterone synthesis and interfere with follicle development. Recent studies shown how the gut microbiota composition significantly alters in patients with PCOS compared with women without PCOS. Furthermore, gut microbiota disorders are closely associated with clinical conditions such as obesity and Insulin Resistance. However, the mechanisms of gut microbiota in PCOS patients are not fully understood. [3][7][5]

Aim and Objectives:

The main aim and objectives of this review are as follows: 1) Role of Insulin Resistance in the development of PCOS. 2) Correlation between gut microbiota and his PCOS. 3) Potential mechanisms underlying the association between Iinsulin Resistance and gut microbiota in PCOS patients; and 4) A potential means of overcoming gut microbiota abnormalities with the aim of improving the management of PCOS patients.

Methodology:

To write this review, a systemic search on various concepts has been performed in PubMed and Google Scholar databases. The articles used here reported the concept of relationship between gut microbiota and PCOS. Specific terms such as dysbiosis, insulin

resistance were filtered and taken from the databases. Selection criteria for research articles and papers were restricted to 5-year window which consists mainly evidence-based and systemic reviews.

Results:

A summary of around 9 articles were included and based on that a script was made which discusses the following topics:

☐ Concept of Insulin resistance

☐ Relationship between insulin resistance and PCOS

☐ Concept of PCOS and gut microbiota

☐ PCOS and microbiota composition and diversity

☐ Potential mechanism of insulin resistance in relation to gut microbiota due to PCOS and treatment for this

Overview of the relationship between Insulin Resistance and PCOS

Insulin resistance is considered as one manifestation of polycystic ovary syndrome (PCOS) that causes ovulatory dysfunction and development of endometrial disorder leading to infertility.It has shown long-term and detrimental effects on metabolism of patients with PCOS. Irrespective of obesity, it is seen that 50% of patients with PCOS have insulin resistance. The development of follicle in patients with PCOS- ovulation or oligovulation is a common symptom of PCOS. Insulin Resistance along with redeeming hyperinsulinemia is one such intrinsic factor in the development of PCOS by producing the excess androgen. Excess insulin production triggers insulin receptor of pituitary gland, to release luteinizing hormone (LH), and promote secretion of androgen by ovary and adrenal gland. It inhibits the synthesis of hepatic sex binding globulin (SHBG), and increase the levels of free testosterone (T). Excess androgen secretion leads to hirsutism, acne, alopecia symptoms, and inhibits the growth and development of ovarian follicles which is the most common reason of barren secondary to ovulatory dysfunction. Moreover, insulin is directly regulated to the development of the ovarian follicle and hormone secretion through the insulin receptors in the follicle membrane cells. It also enhances activity of insulin-like growth factor-1 (IGF-1) receptor in the ovary which increases its levels of free IGF thereby promoting the production of androgen. A change in endometrial function is shown as one significant cause of low fertility in PCOS patients where insulin resistance is a characteristic metabolic feature that affects the physiological function in uterine endometrium and receptivity(ER). Patients with PCOS show worst endometrial receptivity than that of normal women. This condition leads to a reduction in the levels of glucose transporter 4(GLUT-4) and other glucose transporter proteins in the later stage of endometrial hyperplasia, leading to the shortage of glucose supply in endometrial cells leading the onset of endometrial development disorder. In

fact, the hyperandrogenism induced by insulin resistance inhibits the growth and activity of endometrial cells by interfering with glucose metabolism and inhibiting decidual differentiation. [2]

Poor ER is aggravated in PCOS with redeeming insulin resistance and is closely associated with glucose and lipid metabolism disorders, amino acid metabolism, and other adverse consequences. Dyslipidemia is the most common metabolic disorder in PCOS patients with a prevalence rate of 70%. Insulin Resistance reduces ability of the insulin to inhibit lipase leading to a high level of free fatty acids and risk of obesity and cardiovascular diseases in PCOS patients. Hyperinsulinemia inhibits lipolysis through fibrinolysis inducing arterial hypertension. Reports shown that patients with PCOS are 5 to 7 times more likely to develop T2DM than patients without PCOS and the possible explanation was abnormal glucose metabolism. [6]

Gut microbiome contributes to insulin resistance. Several studies designed and shown that gut microbiota plays a significant role in the development of obesity, obesity-associated inflammation, and insulin resistance. Cani et al. proposed that "endotoxemia" which is produced by gut microbiome is an essential factor in initiating inflammatory activities leading to obesity and insulin resistance. Gut microbiome promotes energy absorption by enhancing the triacylglycerol synthesis and inhibiting the fatty acids oxidation. This affects the energy balance of the human body leading to Insulin Resistance. Dysbiosis of gut microbiota increases intestinal mucosal permeability and a variety of inflammatory mediators such as lipopolysaccharide (LPS), and the branch-chain amino acid (BCAA) in the intestinal microflora. The BCCA activates the immune response of the body, whereas the inflammatory mediators activate toll-like receptors 4 (TLR4), resulting in reduced sensitivity to insulin. [5][6]

PCOS and gut microbiota

Several studies demonstrated that microbiota dysbiosis occurs in PCOS patients. A change in the overall composition of the gut bacteria results in a decrease in alpha and beta diversity. Moreover, changes in the relative abundances of certain gut bacteria have been associated with clinical implications of PCOS [4] [7]

PCOS and microbiota diversity

Alpha(α) diversity is correlated with the health of an ecosystem which is used to estimate the abundance of species in that environmental community. Beta (β) diversity on the other hand is known as the variety of the ecological environment. Studies reported a decrease in alpha diversity as well as a change in β diversity in patients with PCOS which leads to intestinal dysfunction thereby concerning insulin levels, glucose tolerance levels, and androgen levels, which worsens the symptoms of PCOS.

PCOS and microbiota composition

Many studies proved an integral relationship between PCOS and the abundance of some gut microbiota at phylum, family, and genus levels. Gut bacteria that mainly exists are *Firmicutes* and *Bacteroides*, followed by *Actinomycete, Proteobacteria*, and *Clostridium*. A significan changes in intestinal flora was in letrozole-induced PCOS model in mice, including a significant decrease in the total intestinal microbial species count and phylogenetic richness as well as reduction in Bacteroides and an increase in Firmicutes. This rise is closely caused by the occurrence and development of obesity, T2DM, and metabolic syndrome. It is known that *Lactobacilli* and *Bifidobacteria* are beneficial bacteria that function by enhancing immunity and nutrient absorption however found reduced in PCOS patients, Roseburia, and Ruminococcus) that had a lower abundance in PCOS patients. The abundance of Faecalibacterium (specifically Faecalibacterium Prausnitzii), Bifidobacterium, and Blautia were found lower in PCOS patients which might lead to changes in production of short-chain free fatty acids (SCFAs) affecting the integrity of the intestinal barrier. As a fact, gram-negative bacteria are known for producing lipopolysaccharides (LPS), which induce inflammation, insulin resistance, and obesity by leaking into the blood-stream. The gram-negative bacteria belonging to the genera Bacteroides and Escherichia/Shigella were found significantly increased in the gut of PCOS patients accompanied by a reduction in the levels of glycodeoxycholic and tauroursodeoxycholic acids which indicates that bile acid metabolism is one of the critical metabolic pathways affected by the gut microbiota changes in. Intestinal flora metabolism is found closely associated with the occurrence and development of diseases. [8][9]

Potential mechanism underlying the association between IR and gut microbiota of PCOS

The pathogenesis of PCOS is still uncertain though majorly focused on genetics, immunity, androgen exposure, and so forth. Intestinal flora on the other side is an indispensable "microbial organ" of the human body that plays a critical role in sustaining human health. The signal pathway behind the insulin receptor shows crossover effect with the signal transduction of chronic subclinical inflammation. In fact, the occurrence of insulin resistance is associated with endotoxemia, chronic inflammatory response, short-chain fatty acids, and bile acid metabolism which results in a significant imbalance in the intestinal flora among PCOS patients. [7]

Endotoxemia: PCOS is a female reproductive endocrine disease which is related to chronic gut barrier-endotoxemia-inflammation mechanism. Endotoxemia play a role in the pathogenesis of PCOS by initiating inflammatory activity via the production of lipopolysaccharides in the intestinal flora and has an endotoxin effect.

Lipopolysaccahrides when absorbed into the blood, protein (LBP) binds to CD14 toll-like receptor complex (TRL-4) on the surface of innate immune cells thereby activating the downstream signaling pathway. This activation then interferes with insulin receptor function which drives up serum insulin levels. At the same time, the presence of a "leaky gut" generates an increase in serum tumor necrosis factor-alpha (TNF-α) and interleukin6 (IL-6) mediated by endotoxin-induced activation of macrophages. The expression of TNF and IL-6 is highly increased among PCOS patients and can increase fasting blood glucose and insulin levels. This implies that when intestinal barrier function is impaired, endotoxin produced by intestinal flora enters the blood causing chronic ovarian inflammation and insulin resistance which then promotes the occurrence and development of PCOS.[1][3]

Short-chain free fatty acids (SCFAs): The importance of fatty acids (FA) among PCOS patients was reported and adipose tissue (AT) was the best indicator. Adipose tissues are fat storing organ with important endocrine and metabolic functions. Fatty acids especially short-chain ones like trans fatty acids and saturated fatty acids plays significant role in the development of PCOS through their stimulating action. Stearoyl- CoA desaturase (SCD1) is an endoplasmic reticulum enzyme responsible for catalyzing the biosynthesis of MUFA from SFA either synthesis or derived from the diet and is found elevated among PCOD patients due to disruption of n3:n6 with this expression. [4]

Bioconversion of bile acids: The bile acid pool synergises between host and intestinal flora thereby affecting the growth and the proliferation of the intestinal flora to shape the microbial community in the intestine. Bile acids is seen regulating the gut microbiome, and vice versa and these mutual influences are heavily involved in the regulation of multiple diseases such as PCOS and Insulin Resistance. The intestinal flora as well as bile acids of patients with PCOS are significantly different from healthy individuals. Species such as Lactobacilli, Streptococcus, and Escherichia coli are higher in PCOS patients; and Ruminococcus, Lachnospiraceae, and Prevotella are lower. Bile acids affects the regular functioning of ovarian cells causing dysfunction in the patients. The intestinal ecological balance is somewhat disturbed and then decrease in TDCA and GDCA levels is seen with a reduction in the activity of transcription factor GATA-binding protein 3.This reduces the secretion of IL-22 by intestinal type-3 natural lymphocytes and consequently elevation of brown inhibits the inflammatory response of ovarian granulosa cells, modulating ovarian function and insulin sensitivity in polycystic ovary syndrome. [8]

Amino acid synthesis: Amino acids and their derivatives serves as signalling molecules in regulating endocrine and immune functions as well as multiple metabolic pathways. An irregularity in

amino acid homeostasis contributes many endocrine and metabolic disorders. Significant changes of amino acids were found in the plasma, serum, urine and follicular fluid of women with PCOS. An association is seen between insulin resistance and deregulated metabolism of aromatic amino acids (AAA) such as phenylalanine and tyrosine as well as branched chain amino acids (BCAA) (isoleucine, valine and leucine), and different carnitines. This interplay between BCAA and lipids is said as a contributor to the development of insulin resistance in obese individuals as well as PCOS.[3][4][5]

Hyperandrogenism:

Hyperandrogenism is a fundamental symptom of polycystic ovarian syndrome (PCOS). Approximately three-quarters of women with anovulatory infertility have PCOS where one-third of women with secondary amenorrhea and around 90% with oligomenorrhea. Hyperandrogenism is characterized with elevated serum concentrations of androstenedione, testosterone as well as dehydroepiandosterone sulphate. They are three androgens produced excessively in ovary during PCOS especially in those women who do not have congenital adrenal hyperplasia. This androgenic effects occurs through suppression of lutenizing hormone secretion by progestin component and inhibition of ovarian androgen production. [7]

Gut-brain peptides: PCOS is a complex yet common disorder accompanied with insulin resistance, obesity and glucose intolerance. Gut, brain and metabolism are highly connected with each other specially in PCOS. Ghrelin, the only circulating orexigenic hormone is shown in decreased or unaltered levels in PCOS. Peptides associated with this hormone are shown in suppressed levels. [2]

The treatment approach in PCOS

The vital role of intestinal flora is regulating human metabolism and energy storage. Much focus is directed to intestinal bacteria as a new strategy for the treatment of obesity and related metabolic diseases. Lifestyle change involving exercise is the first step to treat PCOS. Also, changes in diet brings rapid changes in the relative abundance of species making up the intestinal flora. A well balanced diet will help increase production of short-chain fatty acids which reduces incidence of chronic inflammation. Foods rich in sugar or salt are one of the inducers of PCOS causing intestinal flora imbalance and triggering chronic inflammation, insulin resistance, and production of androgen. The vivid relationship between exercise and intestinal flora is seen currently. Intestinal microorganisms and their metabolites regulate PCOS-related ovarian dysfunction and insulin resistance. Transplantation of Bacteroides vulgatus infected fecal microbes in mice resulted in ovarian dysfunction, insulin resistance, changes in bile acid metabolism, decreased secretion of interleukin-22, and infertility. Probiotics supplementation could reduce fasting blood glucose, serum insulin, HOMA-IR, triglyceride,

and cholesterol in PCOS patients. Consumption of probiotic Bifidobacterium Lactis V9 promotes the growth of SCFA producing microorganisms (such as Faecalibacterium Praussnitzii, Butyriminas, and Akkermansia). Moreover, changes in PYY and ghrelin levels caused fluctuations in sexual hormone levels secreted by the thalamus and thalamus through the gut-brain axis. Guo et al. treated PCOS rats models with Lactobacillus and fecal microbiota transplantation (FMT) from healthy rats. They observed an improvement in the estrous cycles in all eight rats in the FMT group. Also, ovarian morphologies in six of the eight rats in the Lactobacillus transplantation group with decreased androgen biosynthesis were normalized. The composition of the gut microbiota was restored in both FMT and Lactobacillus treated groups. The new composition of the gut microbiota had an increased abundance of Lactobacillus and Clostridium and a decreased abundance of Prevotella. Considering these results, FMT may become a new direction in the treatment of PCOS. [9]

Conclusion

Intestinal flora being an exogenetic material regulates expression of host genes thereby affecting occurrence of PCOS. It participates in the occurrence and development of PCOS through various links and pathways. Furthermore, it may even affect the occurrence and development of insulin resistance in women with PCOS. Hence, it is mandatory to further detect and analyze specific functional bacterial profiles related to the occurrence and development of PCOS on an individual basis. There is a need for further research to determine whether the manipulation of the intestinal microbiota useful in the treatment of PCOS. It is also necessary to explore the potential use of probiotics and fecal transplant therapies in the treatment of the same.

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