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# Concept and Therapeutic Approach of Intermediate Hyperglycemia with Special Reference to Unani Medicine

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***Authors' contributions***

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

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## ABSTRACT

Intermediate Hyperglycemia is a category of glucose tolerance representing an intermediate stage between normal glucose tolerance (NGT) and diabetes. Within this category are two subcategories: impaired fasting glucose (IFG; 100 –125 mg/dl) and impaired glucose tolerance (IGT; defined as a 2-h oral glucose tolerance test (OGTT) plasma glucose concentration of 140 –199 mg/dl). Intermediate Hyperglycemia is not specifically mentioned in Unani medicine, however some classical Unani physicians have described the initial symptoms and factors leading to the pathology. In Unani medicine the risk factors are described in terms of '*Su-e-mizaj*' as per the concept of Tibb. So, it is considered in the context of *Zeyabutus* which is described as a disease which develops due to *Su-e-mizaj haar* (abnormal hot temperament) by the majority of scholars. The two major pathophysiologic defects responsible for losing glucose tolerance are insulin resistance and β-cell glucose insensitivity, both appearing in subjects of Intermediate Hyperglycemia. Symptoms mentioned in Unani medicine may be increased frequency of micturition (ants and flies are attracted to urine), increased thirst, nocturia, dryness of mouth and whole body, fatigue, loss of weight, malaise, cramps in lower extremities.

The drug based approach for management of Intermediate Hyperglycemia is associated with inherent drawbacks, including toxicity, tolerability, cost and efficacy. Oral hypoglycemic drugs are

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also associated with various side effects as Biguanides cause gastrointestinal upsets, anorexia, nausea, diarrhea and lactic acidosis. There are a number of single Unani drugs like Jamun (*Syzigium cuimini*), Karela Bark or Bitter Gourd (*Momordica charantia*), Neem (*Azadirachta indica*), Methi (*Trigionella foenum*), Bael Leaves (*Aegle marmelos*), Kalonji (*Nigella sativa*), Tabasheer (*Bambusa arundinaceae*), *Gurmar* booti (*Gymmema sylvestre*) and compound formulations like *Qurs Ziyabetus, Qurs Tabasheer, Qurs Kafoor*, *Qurs Gulnar.*

*Keywords: Intermediate hyperglycemia; impaired fasting glucose (IFG); impaired glucose tolerance (IGT).*

## 1. INTRODUCTION

The overall prevalence of Intermediate Hyper-glycemia/prediabetes to be 10.3% (WHO criteria) or 24.7% (ADA criteria), depending on which definition was used.

Intermediate Hyperglycemia and Prediabetes are the term used for each other, because it refers to an intermediate stage between normoglycemia and apparent Diabetes Mellitus. It is a type of metabolic disorder with slight increase in blood glucose level from normal but not reaching up to the level of Diabetes Mellitus [1]. Prevalence of intermediate hyperglycemia varied considerably according to the definition used. The prevalence of IGT (20.3%) was similar to that of IFG based on the WHO criteria (19.1%). However, the prevalence of IFG based on the ADA criteria was much larger (52.6%). Regardless of the criteria used, these intermediate states of hyperglycemia were higher in men. When classified by $HbA_{1C}$ values, intermediate hyperglycemia was present in 16.1% (ADA definition) and in 7% and was more common among women, both men and women, the frequency of IGT increased by age categories [2].

The World Health Organization (WHO) in 2006 has recommended the term Intermediate Hyperglycemia to describe glycaemic levels between 'normal' glucose tolerance and diabetes. The term 'pre-diabetes' is discouraged to avoid any stigma associated with the word diabetes and the fact that many people do not progress to diabetes as the term implies [3].

Intermediate Hyperglycemia is a category of glucose tolerance representing an intermediate stage between normal glucose tolerance (NGT) and diabetes. Within this category are two subcategories: impaired fasting glucose (IFG; defined as a fasting plasma glucose concentration of 100 –125 mg/dl) and impaired glucose tolerance (IGT; defined as a 2-h oral glucose tolerance test (OGTT) plasma glucose concentration of 140-199 mg/dl) although both subcategories increase the risk for diabetes [4].

Intermediate Hyperglycemia is not specifically defined as a disease in Unani medicine, however some classical Unani physicians have described that initial symptoms and factors leading to the pathology. In Unani medicine the risk factors are described in terms of '*Su-e-mizaj*' as per the concept of Tibb. In this context diabetes is described as a disease which develops due to *Su-e-mizaj haar* (abnormal hot temperament) by the majority of scholars [5,6].

Public health programs focused on increasing personal awareness of risk, community support and education, and government resources are necessary to slow the progression of Intermediate Hyperglycemia to T2DM. Importantly, health care systems need to recognize "Intermediate Hyperglycemia" as a disease and to use this term to promote programs. Diet and exercise are first line intervention along with oral hypoglycemic drugs to achieve the goal of improving glycemic control and preventing both microvascular and macrovascular health risk factors. With above facts both dietary and lifestyle changes can improve blood sugar level in Intermediate Hyperglycemia. Its incidence is increasing day by day and to overcome the problem of Intermediate Hyperglycemia. Several efforts have been introduced in the modern system of medicine. But most of these efforts are not effective and fail to prevent complications of Intermediate Hyperglycemia and diabetes.

## 2. CONCEPT OF INTERMEDIATE HYPER-GLYCEMIA IN UNANI MEDICINE

According to Hakeem Azam khan '*Ziabetus haar*' is the disease which is mentioned as diabetes mellitus type 2 in the present era [7]. In Al-akseer he described that the initial symptoms of

diabetes are having polydipsia without dehydration, frequent micturition without burning along with watery urine having less viscosity [6]. Almost similar symptoms are mentioned by *Ibn-e-Sina* who also described polyuria as the first symptom of diabetes which later on progressed to *Diq* (Asthenia) [5]. The classical Unani scholars, *(Razi* 865AD, *Ibn-e-Sina* 980AD) have well recognised Z*iabetus* (diabetes) and were familiar with the manifestations of the diabetes. They described most of the symptoms of diabetes such as excessive thirst, frequency of urination, dribbling of urine, urine appearing white, losing its consistency to resemble water, excessive micturition without burning sensation, incontinence of urine [6,8,9].

The important etiological features of Ziabetus (diabetes) mentioned in Unani are following: *Zauf-e-Gurda* (Weakness of Kidney), *Ittesa-e-Gurda wa Majra-e-Baul* (Dilatation of Kidney and Tubule), *Buroodat-e-Badan, Jigar wa Gurda*, *Su-e-Mizaj Haar Gurda* (Hot derangement in temperament of kidney) and *Su-e-Mizaj Barid Gurd*a (Cold derangement in temperament of kidney). It is a disease in which the patient feels excessive thirst without fever and dryness and consumed water is passed out through the kidneys immediately after intake by the patient without any metabolic change and patient still feels thirsty. *Zakariya Razi* in *Kitab-ul-Hawi-fil-Tib* says that the patient of diabetes complains of polydipsia, whereas, the consumed water is passed out as such. He further mentions other symptoms associated with this disease like polyuria, polydipsia, even nocturia and incontinence of urine [8].

## 3. PATHOPHYSIOLOGY OF INTERMEDIATE HYPERGLYCEMIA

Normally the glucose system is highly homeostatic, swinging in plasma glucose concentrations rarely exceeding mmol/L (54 mg/dl), Plasma glucose concentration represents a balance between entry of glucose into and exit from the circulation via excretion. Disturbances in the homeostasis (either excessive release or defective removal or combination of the two result in an increasing glucose level). Abnormality in glucose and insulin concentration and dynamics occurs constantly and insidiously with the development towards Type 2 diabetes [10]. The two major pathophysiologic defects responsible for losing glucose tolerance are insulin resistance and β-cell glucose insensitivity, both appearing in subjects of Intermediate hyperglycemia/ Pre-diabetes [11].

*Jalinoos* (Galen) described it as a disease specific to kidneys because of weakness in their retentive ability. He attributed that the weakness of *quwwat-e-mughayyarah* may be a causative factor of diabetes. He mentioned that, when hot temperament is associated with moisture, then absorption (into the kidneys) is less, urine is dark in colour, viscous and, if cold temperament is predominant along with dryness, then the power of absorption is very strong and this is the most lethal form of diabetes [12,13].

*Zakariya Razi* in *Al-Hawi-fil- Tib* states that this disease is basically caused due to abnormal hot temperament of the kidneys. This hot temperament affects the bladder also. Due to the increased heat, the kidneys absorb a lot of fluids from the gastro-intestinal tract. And also, due to weakness of *quwwat-e-masika*, the kidneys are not able to retain these fluids and they are immediately diverted to the bladder, and excreted as such. The loss of fluids is again responsible for increasing the already abnormal hot temperament. This gives rise to a vicious cycle of intake and excretion [8]. According to *Ibne Nafees* in diabetes *quwwate- masika* of the kidneys is weakened due to the abnormal hot temperament, therefore, they are unable to retain the fluids in the body and the *quwwat-e-dafi'a* is stimulated and it expels the fluids immediately after intake. Thus the cycle of absorption (into the kidneys) and excretion continues. On this basis, it has been named *dulaab* (water-wheel) and *dawwarah* (whirling etc). *Ibne Sina* termed the disease "*aldulab*" (water wheel) and "*Zalqul Kulliya*" (diarrhea of the kidneys) also described the complications as mental troubles, impotence, gangrene. *Ibne Sina* was the first who wrote a differentiating feature of *Ziabetus* (Diabetes) associated with emaciation from other causes of polyuria [12].

## 4. RISK FACTORS

There are several risk factors which are responsible for the development of Intermediate Hyperglycemia such as: Environmental factors, Diet, Physical inactivity, Smoking, Hereditary [14, 15,16]. Other risk factors responsible for the development of Intermediate Hyperglycemia are: Family History, Obesity, Sedentary lifestyle, Race or ethnicity, having hypertension, cardiovascular diseases, previously identified raised IGT, IFG, and/or metabolic syndrome,

Increased levels of triglycerides, low concentrations of HDL cholesterol, history of gestational diabetes etc.[1,17,18].

## 5. ETIOLOGY OF INTERMEDIATE HYPER-GLYCEMIA

The etiology of disease is considered to be seated in the kidneys and the liver. *Ziabetus* is caused by one of more of the following factors:

**a. *Su-e-Mizaj Haar kulliya* (Hot derangement in the temperament of kidneys)**

Kidneys absorb water in an excess amount from circulation due to excessive hotness or derangement in temperament, so they cannot retain much amount of fluid and pass in the form of urine frequently (polyuria) and the patient drinks water frequently (polydipsia) to overcome his thirst [9].

**b. *Su-e- Mizaj Barid kulliya* (Cold Derangement in Temperament of Kidney)**

Sometimes, Ziabetus develops due to excessive exposure of cold to kidneys that may lead to *Sue mizaj barid* (cold derangement in temperament) [9,19].

**c. *Zoaf-ul-Kulliya* (Weakness of Kidneys/ Renal insufficiency)**

Water cannot be retained properly due to the weakness of kidneys and their *Quwate masik* [19].

**d. *Barudat-e-kabid wa kulliya* (Cold Derangement in Temperament of Kidneys and liver)**

It is due to the excessive exposure of the whole body or liver or kidneys to cold, which leads to sue mizaj barid (cold derangement in temperament [7,19,20].

***e. Ittisa-ul-kulliya wa Majrā-e-Bauwl* (Dilatation of Kidneys and urinary tract)**

Water cannot be retained for long or required time due to dilatation of *kulliya wa Majrae Baul* (Dilatation of Kidneys and Tubules) so it is passed out rapidly [7,19].

In addition to the above mentioned causes of *Ziyabetus*, some other causes are also described by different Unani authors in the classical Unani literature that include:

a) Impaired renal functions [20]
b) Cirrhosis of kidney, renal cortical atrophy [21]
c) Neurological disturbances [20]
d) Psychological causes [21]
e) Obesity [20,22]
f) Excessive use of hot foods [20]
g) Alcoholism [20,23]
h) Increased work load [23]
i) Excessive sexual intercourse [20,24]
j) Impaired Pancreatic function [20]
k) Injury on head on 4h ventricle [23]
l) Increased level of sugar in blood [20]

## 6. SYMPTOMS IN INTERMEDIATE HYPER-GLYCEMIA

Intermediate Hyperglycemia/Prediabetes remains undiagnosed for several years because this disease develop without any appearance of symptoms and sign. But sometimes symptoms in Intermediate Hyperglycemia are frequent urination and excessive thirst same as of type 2 diabetes [25].

Unani physicians had good knowledge regarding the clinical features of *Ziabetus* (diabetes) at that time. The clinical features may differ from patient to patient according to severity of disease. Sometimes, it might be possible that patient remain asymptomatic and diagnosed accidentally while going through checkup for some other disease. Unani Physicians have described the clinical features: increased frequency of micturition (ants and flies are atracted to urine), excessive thirst which cannot be easily quenched by water, nocturia, dryness of mouth and whole body, fatigue, loss of weight, malaise, decreased libido and sterility, vaginitis, balanitis, cramps in lower extremities, numbness in hands and feet *Zooban-e-Aza* (Organs and extremities get melted and the secretion is excreted via urine).

## 7. DIAGNOSTIC CRITERIA FOR INTERMEDI-ATE HYPERGLYCEMIA (PRE-DIABETES)

The World Health Organization (WHO) has defined the state of intermediate hyperglycemia using two specific parameters:

Impaired fasting glucose (IFG) defined as fasting plasma glucose (FPG) of 6.1-6.9 mmol/L (110 to 125 mg/dl). Impaired glucose tolerance (IGT)

defined as 2 h plasma glucose of 7.8-11.0 mmol/L (140-200 mg/dl) after ingestion of 75 g of oral glucose load or a combination of the two based on a 2 h oral glucose tolerance test (OGTT) [26]. The American Diabetes Association (ADA), on the other hand has the same cut-off value for IGT (140-200 mg/dl) but has a lower cut-off value for IFG (100-125 mg/dl) and has additional hemoglobin A1c (HbA1c) based criteria of a level of 5.7% to 6.4% for the definition of Pre-diabetes [27].

### 7.1 Diagnosis through Unani Medicine

Diagnosis of Ziabetus Shakari depends on the above mentioned clinical features.

## 8. HEALTH RISKS OF INTERMEDIATE HYPERGLYCEMIA

Likewise diabetes, Intermediate Hyperglycemia may have concomitant damage to organs and produce health risks like: nephropathies and chronic kidney diseases, retinopathy, neuropathies, macrovascular disorders [28,29,30]. Unani physicians were also aware about the complications related to diabetes (Ziabetsus).

a. lbn-e-Sina mentioned that diabetic patients may develop due to loss of body fluids phthisis (*Diq*) and cachexia (*Zooban-e-Aza*) [5].
b. Azam Khan mentioned this disease as very perilous and said that this disease affects elderly people then it becomes almost untreatable [6].

## 9. MANAGEMENT OF INTERMEDIATE HYPE-RGLYCEMIA

Management of Intermediate Hyperglycemia (Pre-diabetes) is broadly classified in two major groups which includes:

Non- Pharmacological Interventions or Life style modifications.
Pharmacological Interventions.

### 9.1 Non-pharmacological Interventions or Life Style Modifications

Modification in lifestyle may serve as keystone of treatment focus on diet, 7% of weight loss and 150 minutes per week of moderate physical activity. Risk of developing diabetes is reduced by 90% in person who lost weight and who meet physical exercise/dietary targets. These results are consistent with Finnish Diabetes Prevention Study in which participants met four or five of their goals. In a study with IFG it has been reported that intensive weight loss is more effective in reducing the conversion of Type 2 diabetes from IFG as compared to less intensive intervention. [31] It has also been noted that sustained loss of 5-10% body weight in obese and overweight patients proven to be effective in preventing progression of Type 2 diabetes from Prediabetes. [32] A modest weight loss (5%-10%) and moderate intensity physical activity (30 minutes) daily) is the mainstay of treatment for subjects with prediabetes. When lifestyle modification is ineffective, it is advised in subjects who are at high risk due to high chance of progressive deterioration of glucose control. Also, in the patients who are unable or unwilling to engage in lifestyle modifications or those have inadequate response to lifestyle change, pharmacotherapy is advised [31].

### 9.2 Pharmacological Interventions

There are numerous groups of pharmacological interventions include anti-hyperglycemic drugs, anti-obesity medication and others like Renin-angiotensin blockers and Statins have been studied in context of management for Prediabetes [32]. The drug based approach for management of Intermediate Hyperglycemia (prediabetes) is associated with inherent drawbacks, including toxicity, tolerability, cost and efficacy. Oral hypoglycemic drugs are also associated with various side effects as Biguanides cause gastrointestinal upsets, anorexia, nausea, diarrhea and lactic acidosis. Similarly sulfonylureas cause weight gain, thiazolidinediones enhance the risk of myocardial infarction and α-glucosidase inhibitors have side effects like flatulence, abdominal comfort, bloating, diarrhoea etc.

### 9.3 Management of Intermediate Hyper-glycemia in Unani System of Medicine

#### 9.3.1 Line of Treatment (*Usool-e-Ilaj*)

**a. Correction of *Su-e-Mizaj***

Unani line of treatment may be effective for correction of kidney and correction of its temperament (*Su-e-Mizaj*) and could be preventive in progressing the disease further.

**b. Removal of predisposing cause**

Remove the predisposing factors which are responsible for this disease.

**9.3.2 Ilaj (Treatment)**

Therapeutic approaches for *Ziabetus* in Unani medicine can be broadly classified into three main categories.

- Dietary modifications
- Lifestyle modifications
- Ilaj-bil-tadbeer (Regimental therapy)
- Pharmacotherapy
  - Use of Mubarridat (Refrigerant) and Murattibat (Humectants)
  - Use of Habisat wa Qabizat (Astringent and styptics)
  - Taskeen-e-Atash (Quenching of the thirst)
  - Taqwiyat wa Tabreed-e-Kulliya (Strengthening and cooling of kidneys)
  - Use of Dafa-e-Ziyabetus Advia (Anti-diabetic drugs)

*9.3.2.1 Dietary modifications*

- Avoid refined cereals.
- Give more weightage to fibrous foods.
- Avoid fatty foods.
- Avoid junk, fast and sugary foods.
- Restrict red meat and liquor.
- Foods should be cooked in vinegar.
- They should reduce the amount of food.
- Hot spices should be added in *ghiza* (food) e.g. *Filfil Daraz,Zeera,, Lehsun* because they have *Mulattif*

*9.3.2.2 Lifestyle modifications*

- Physical exercise of appropriate intensity and duration is recommended.
- Excessive sleep should be avoided because of its role in promoting the phlegmatic humour.
- Stress, strain and anxiety should be avoided.
- Avoid sedentary lifestyle.
- Avoid humid and cold environments.

*9.3.2.3 Ilaj-bil-Dawa (Pharmacotherapy)*

In this context, Mubarridat (Refrigerant) and Murattibat (Humectants), Habisat wa Qabizat (Astringent and styptics), Taskeen-e-Atash (Quenching of the thirst), Taqwiyat wa Tabreed-e-Kulliya (Strengthening and cooling of kidneys), Dafa-e-Ziyabetus Advia (Antidiabetic drugs)may be used.

*9.3.2.4 Use of Mubarridat (Refrigerant) and Murattibat (Humectants)*

According to Hippocrate it is a disease of hot and dry derangement of temperament (*Sue- Mizaj haar yabis*) As per the basic concept of *Ilaj-bil-zid* (*Barid-ratab*) is advised. For this purpose cold vegetables and cold fruits are used but these entities should not have the diuretic action etc. [5].

*9.3.2.5 Use of Habisat wa Qabizat (Astringent and styptics)*

*Habis* and *Qabiz* drugs have been used by Unani physicians to control polyuria by increasing the retention power of kidneys thereby decreasing excretion of urine. As far as diet is concerned use of astringent (*Oabizat-wa-Habisat*) foods are advised for diabetic patients. According to Sarabiyun, regimen like *tarteeb badan, aghzia barida* and use of *zimad-e-barid* over kidneys are beneficial [6].

*9.3.2.6 Taskeen-e-Atash (Quenching of the thirst)*

As the diabetic patient suffers from excessive thirst (polydipsia).There is a need to quench thirst in order to provide symptomatic relief to the diabetic patients and to save them from dryness. *Taskeen-e-Atash* (quenching of the thirst) is advised as an early management for diabetes. For quenching thirst, drinking cold water followed by vomiting is advised. Feeling of thirst will decrease. Uses of diuretics are contra-indicated [19].

*9.3.2.7 Taqwiyat wa Tabreed-e-Kulya (strengthening and cooling of kidneys)*

It is advised in order to overcome the hot derangement of temperament of the kidneys. For this purpose it is advised to apply cold liniment (*Zimad-e-Barid*) at the site of the kidneys. Along with this use diets and medicine which are nephro-protective (*Muqawi-e-Gurda Advia-wa-Aghzia*) are also preferred like *Ma-ul-Shaeer* and *Ab-e-Anar.* While according to Jalinoos use of *alkaliser* and *Tabreed-e-Kulliya* should be the way of treatment [5].

*9.3.2.8 Use of Dafa-e-Ziyabetus Advia*

Several Unani physicians like Razi*, Majoosi, Ibn-e-Sina* and *Mohammad Azam khan* had prescribed several medicinal plants either single or as a constituent of compound formulations, for the treatment of *Ziyabetus Shakari* [5,6,8,9].

*9.3.2.9 Single drugs (Mufrad Advia)*

Following single drugs have been used in Unani medicine since ancient times: [5,6,8,19].

a. **Jamun** (*Syzigium cumini*) Jamun seeds control the level of sugar in urine and decrease the Diabetic symptoms. This is the main quality of *Jamun* seeds.
b. **Karela Bark or Bitter Gourd (***Momordica charantia***)**: This plays an important role in the management and prevention of diabetes.
c. **Neem (***Azadirachta* indica**):** Neem is mainly used in purifying blood. It controls the level of sugar in blood.
d. **Methi** (*Trigionella foenum*): This lowers the blood sugar level & good source of **f**ibers.
e. **Binola Seeds or Cotton seeds,**
f. **Bael Leaves (***Aegle marmelos*)
g. **Kalonji** (*Nigella sativa*)
h. **Tabasheer** (*Bambusa arundinaceae*): Regulates the blood sugar due to the presence of natural antioxidants.
i. **Zanjabeel** (*Zingiber officinalis*)
j. ***Gurmar* booti** (*Gymmema sylvestre*)

*9.3.2.10 Compound formulation (Murakab Advia)*

Following Compound formulations (*Murakab Advia*) are used in Unani system of medicine:

i. *Qurs Ziyabetus* [24]
ii. *Safoof-e- Ziyabetus* [33]
iii. *Qurs Tabasheer* [5,19,24]
iv. *Qurs Kafoor* [24]
v. *Diabeat* (Hamdard)
vi. *Qurs Gulnar* [5,19]

## 10. CONCLUSION

Intermediate Hyperglycemia is a new terminology used for the intermediate state between normal glycemic level and hyperglycemic level. In this condition every effort is taken against conversion of Intermediate Hyperglycemia into diabetes mellitus. A conventional method of treatment is effective but produces side effects. In Unani medicine there are a large number of single drugs as well as compound formulations which are very effective particularly in this stage. Some of the Unani drugs are validated but a lot are still required for scientific validation on a large scale.

## DISCLAIMER

The products used for this research are commonly and predominantly used in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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