Mechanism for Reversal of TYPE 2 Diabetes-Dr.G Clinical Practice and Ground Reality

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Contents

• Introduction
• Statistics
• Manifestation of Type 2 Diabetes
• Diagnosis of Type 2 Diabetes
• Complications with Diabetes
• Current Scenario
• Factors Causing Type 2 Diabetes
• Twin Cycle of Type 2 Diabetes
• Challenges in the Treatment of Type 2 Diabetes
• Possible Molecular Mechanisms for treatment of Type 2 Diabetes
• Possible Molecular Mechanisms Explained
• Supplements- Diabetall™ and Diabetplus™
• Way to Reverse Diabetes
• Dr.G Clinical Practice- Analysis of Patient Data
• References
Type 2 Diabetes

- Most common
- Is basically Insulin Resistance
- Inevitably progressive
- Diagnosed in adulthood but currently detected even in youngsters.
- Occurs mainly due to Obesity, Unhealthy eating, Failure to exercise.
- Requires increasing numbers of oral hypoglycaemic agents
- Eventually leads to insulin therapy
- Not absolutely dependent on Exo - Insulin
- Absence of immune Destruction of Beta Cells
- Glycemic due to combined insulin resistance & relative beta cell Failure
- Strong Genetic influence
  - 100% concordance has been seen in identical twins
  - 40% for individuals with positive family history
- Strong environmental reaction
## Statistics

Top 10 countries/territories for the number of people with diabetes (20-79 years) 2013 and 2035 (expected)

<table>
<thead>
<tr>
<th>Country / Territory</th>
<th>2013 (in millions)</th>
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<th>2035 (in millions)</th>
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<td>11.2</td>
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Manifestation of Type 2 Diabetes

Genetics and Sedentary lifestyle

Insulin resistance — IR

β-cell dysfunction — β

Type 2 diabetes
Manifestation of Type 2 Diabetes

1. Food enters into the stomach.

2. The carbohydrates break down and glucose (in pink) is released into the blood stream.
3. Beta cells of the pancreas produce insulin that enable the glucose molecules to enter into the cells for energy production.

4. The cells of our body do not respond to insulin (in blue). This is called as insulin resistance. The glucose molecules cannot get into the cells for energy production.

5. Glucose (and insulin) builds up the blood stream causing elevated blood glucose. This also leads to fatigue (no energy in cells), hunger, thirst and increased urination.
Diagnosing Diabetes

Fasting plasma glucose test (FPG) results

- **Diabetes**: ≥126mg/dL
- **Pre-Diabetes**: 100-125mg/dL
- **Normal**: ≤100mg/dL
Complications with Diabetes

**Acute complications**

- Ketoacidosis
- The hyperglycemic hyperosmolar nonketotic syndrome
- Hypoglycemia

**Chronic Complications**

- Disorders of Microcirculation
- Neuropathies
- Nephropathies
- Retinaopathies
- Macro vascular complications
- Foot ulcers
Complications with Diabetes

- Blockages can occur in more than one vessel.
- Muscle below blockage begins to die.
- Blood flow is blocked.
- Plaque reduces blood flow.
- Blood flows through vessel.
Complications with Diabetes (continued..)

<table>
<thead>
<tr>
<th>Day 1</th>
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<th>Day 3</th>
<th>Day 4</th>
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<table>
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<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
</tr>
</tbody>
</table>
Complications with Diabetes (continued..)

Diabetic Peripheral Neuropathy

Healthy Nerves and Blood Vessels

Nerves and Blood Vessels Damaged by DPN

Unmyelinated nerve fiber

Damaged unmyelinated nerve fiber

Vasa nervorum

Myelinated nerve fiber

Occluded vasa nervorum

Damaged myelinated nerve fiber
Complications with Diabetes (continued..)

- Hemorrhages
- "Cotton-wool" spots
- Neovascularization

Background Diabetic Retinopathy

Proliferative Diabetic Retinopathy
Complications with Diabetes (continued..)
Current Scenario: Social Barriers related to Diabetes

**Urban**
- Changing patterns in the lifestyle in families
- Unhealthy eating habits, e.g. fast foods, etc.
- Frequency of eating out
- Faith in different systems of treatment and frequent changes in treatment

**Rural**
- High rates of illiteracy
- Poverty and different socioeconomic strata
- Multilingual population
- Cultural, religious and customs
- Superstitions and beliefs
- Faith in alternate systems of treatment
- Hesitancy to go to doctors or hospitals
Current Scenario: The Generalized Treatment

- **Diet and Exercise**
  - **Oral Hypoglycemic Drugs**
    - Increased dosage of oral hypoglycemic Drugs
    - Increased insulin resistance- Tablets do not work
    - Increased side effects and organ damage
    - Organ Damage continues and Insulin Eventually stops working
  - What next??

*It is not that diabetes runs in your family, it is just that nobody runs in your family.*
Insulin resistance in muscle is the earliest detectable abnormality of type 2 diabetes. In contrast, changes in insulin secretion determine both the onset of hyperglycemia and the progression toward insulin therapy. The etiology of each of these two major factors appears to be distinct.

**Insulin resistance may be caused by**

- An insulin signaling defect
- Glucose transporter defect
- Lipo-toxicity

**B-cell dysfunction is caused by**

- Amyloid deposition in the islets
- Oxidative stress
- Excess fatty acid
- Lack of incretin effect
Factors causing T2 Diabetes

- Increased Secretion of insulin to compensate for insulin resistance
- High circulating free fatty acids
- Chronic hyperglycemia
- Glucotoxicity
- Lipotoxicity
- Lack of Incretin Effect
- Reactive Oxygen Species

Pancreas

β-cell dysfunction

β-Cell deposition of amyloid
Twin cycle of Diabetes

Positive Calorie Balance

Pre-existing Muscle Insulin Resistance

Liver Fat

VLDL triglyceride

Islet triglyceride

Liver Cycle

Resistance to insulin suppression of Glucose production

Basal Insulin secretion

Plasma Glucose

Insulin Response to Ingested Glucose

Pancreas Cycle

Postprandial Glucose
## Challenges in the treatment of Diabetes:

<table>
<thead>
<tr>
<th>Complications</th>
<th>DIABETIC TREATMENTS AVAILABLE</th>
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<tr>
<td></td>
<td>Insulin</td>
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<tr>
<td>Hypoglycemia</td>
<td>✔️</td>
</tr>
<tr>
<td>GI side effects</td>
<td>✔️</td>
</tr>
<tr>
<td>Lactic Acidosis</td>
<td>✔️</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>✔️</td>
</tr>
<tr>
<td>Edema</td>
<td>✔️</td>
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</table>
Can any existing medication address all the pathways??

**Pathways for Reversal of T2D**

- IR↓
- Glycolysis↑
- GLUT1↑
- GLUT4 translocation↑
- HNF-4α mRNA↑
- PPARγ↓, PPARα↑
- Beneficial bacteria↑ (Bacteroidetes↑)
- Harmful bacteria↓ (Firmicutes↓)
- PKC↑
- InsR mRNA↑
- IR↓
- AMPK Phosphorylation↑
- IR↓
- AMPK Pathway activation
- α-glucosidase↓
- Reversed IRS phosphorylation
- GLP-1↑
- Anti oxidation
- MDA, SOD, AR, ↓
- GSH-Px, GSH↑
- Oxidative stress↓
- TNF-α, IL-6, Inos, MCP-1, CRP, COX-2↓
- Glucolipid metabolism regulation
- Gut barrier function↑
- Glucose uptake↑
- Glycolysis↑
- GLUT1↑, RNP4↓
- InsR mRNA↑
- PKC↑
- AMPK Phosphorylation↑
- IR↓
- glycolysis↑
- AMPK Pathway activation
- α-glucosidase↓
- Reversed IRS phosphorylation
- GLP-1↑
- Anti oxidation
- MDA, SOD, AR, ↓
- GSH-Px, GSH↑
- Oxidative stress↓
- TNF-α, IL-6, Inos, MCP-1, CRP, COX-2↓
- Glucolipid metabolism regulation
- Gut barrier function↑
**Possible Mechanisms : Explained**

1. **AMPK-5' adenosine monophosphate -activated protein kinase**
   - **GLUT 4 Translocation**
   - **GLYCOLYSIS**

**Zingiber officinale and Berberis aristata**

- The ingredients of Diabetall and Diabetplus may act on AMPK by phosphorylating it.
- This increase in Kinase activity starts a transport activity of glucose to 3T3-L1 adipocytes and GLUT4 translocation.
- This leads to increase in glycolysis and blood glucose level decreases.
Possible Mechanisms: Explained

2. 

**Activation of HNF-4α** (Hepatocyte nuclear factor 4 subunit α) 
activation of transcription factor HNF-4α and increase in activity of mRNA 

**Hepatic Gluconeogenesis** 

**Momordica charantia, Berberis aristata, Cumini synzygium** 

- HNF-4α (Hepatocyte nuclear factor 4 subunit α) is a gene which acts as a regulator of gluconeogenic enzymatic activity. 
- Ingestion causes activation of transcription factor HNF-4α and increase in activity of mRNA. 
- This in turn leads to decrease in hepatic gluconeogenesis.
There are three subunits of PPARs (Peroxisome proliferator-activated receptors) that are involved in gene regulation i.e. α, δ, γ expressed in tissues of liver, kidney, heart and others. They modulate in liver by increasing the protein expression of PPAR-α and PPAR-δ and decreasing PPAR-γ. This increase and decrease in expression of PPARs subunits regulate glucolipid metabolism and helps in improving lipid metabolism and will have a therapeutic effect which might be exhibited by Diabetall and Diabetplus.
Another possible mechanism might be the regulation of gut microbiota by increasing the beneficial bacteria (Bacteroidetes) and decreasing harmful bacteria (Firmicute).

It shows antimicrobial activity by activating various inflammatory pathways like lipopolysaccharides (LPS) and CD14/TLR-4 (Toll-like receptor-4).

**Berberis aristata**
Possible Mechanisms: Explained

5. Pro-inflammatory cytokines: Tumor necrosis factor-α (TNF-α), Interleukin-6 (IL-6), inducible nitric oxide synthase (iNOS), monocyte chemoattractant protein-1 (MCP-1), C-reactive protein (CRP), and cyclooxygenase-2 (COX-2).

Zingiber officinale, Curcuma longa, Pterocarpus marsupium, Berberis aristata, Cinnamomum Zeylanicum, Ocimum Sanctum

• Diabetall and Diabetplus have anti-inflammatory effects which have been seen both in-vitro and in-vivo by regulation of the pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), Interleukin-6 (IL-6), prostaglandins (PGs), inducible nitric oxide synthase (iNOS), matrix metalloprotease 9 (MMP9), monocyte chemoattractant protein-1 (MCP-1), C-reactive protein (CRP), and cyclooxygenase-2 (COX-2).
• These are also widely implicated as a causative factor in obesity associated insulin resistance.
Possible Mechanisms: Explained

- Malondialdehyde (MDA), aldose reductase (AR)
- Glutathione (GSH), glutathione peroxidase (GSH-PX), and SOD (superoxide dismutase)
- Oxidative Stress
- Insulin Resistance

Lawsonia Inermis, Rosmarinus officinalis, Pterocarpus marsupium, Cassia fistula, Azadirachta indica, Berberis aristata, Cinnamomum Zeylanicum, Ocimum Sanctum

- The supplements perform a major role as antioxidants having inhibitory effects on oxidative stress which is shown by decrease in their markers such as malondialdehyde (MDA), which is increased during oxidative stress and aldose reductase (AR).
- The ingredients in the supplements could have a role in increasing GSH-PX (glutathione peroxidase), glutathione (GSH) which often declines during oxidative stress and SOD (superoxide dismutase).
Possible Mechanisms: Explained

7. \( \alpha \)-glucosidase - intestinal glucosidase → breakdown of the starch and disaccharides → INTESTINAL ABSORPTION OF GLUCOSE

Salacia reticulata, Syzygium cumini, Momordica charantia, Cordifolia tinospora, Berberis aristata, Salacia Oblonga

\( \alpha \)-glucosidase is an intestinal glucosidase which acts upon 1,4-alpha bonds. It helps in the breakdown of the starch and disaccharides.
Possible Mechanisms: Explained

8. Glucagon like peptide-1 (GLP-1) - pro-glucagon

GLYCOLYSIS

INSULIN RESISTANCE

Gymnema sylvestre, Trigonella foenum graecum, cordifolia tinospora, Cinnamomum Zeylanicium

Glucagon like peptide-1 (GLP-1) is a pro-glucagon which improves the activity of the islet cells through a protective mechanism.
A reduced strength of insulin signaling via the insulin receptor substrate (IRS)-1/phosphatidylinositol (PI) 3-kinase pathway, results in diminished glucose uptake and utilization in insulin target tissues.
Possible Mechanisms : Explained

10. Zingiber officinale and Berberis aristata

Decrease in Insulin resistance (IR) is also seen with the activation of AMPK (5' adenosine monophosphate-activated protein kinase) pathway which leads to an increase in glycolysis.
**Possible Mechanisms : Explained**

11. **Berberis aristata**

- *Berberis aristata* might also cause an induced InsR gene expression through a protein kinase C (PKC)-dependent activation of its promoter.
- This causes an increased InsR (insulin receptor) messenger RNA (mRNA) and protein expression.
- This results in a reduced insulin resistance.
Possible Mechanisms: Explained

Momordica charantia, Trigonella foenum graecum and Berberis aristata

• Another possible mechanism could be inhibition of retinol binding protein 4 (RBP4)
  • an upregulation of transportation of glucose GLUT1 which in turn causes increase in glucose uptake by the cells.
  • This is an effective way of glucose sensitization.
Vitamins

**Biotin:** Improves glucose metabolism and is helpful in Peripheral Neuropathy.

**Folic acid:** is essential in the reduction of Homocysteine- a byproduct of oxidation.

**Vitamin D3:** Plays a very important role in glucose metabolism.

**Methylcobalamin:** Is critical for the nervous system and is very helpful in the prevention and management of Diabetic Neuropathy.

**Benfothiamine (fat soluble form of Thiamine):** Benfothiamine is extremely beneficial in Diabetic Retinopathy and Peripheral Neuropathy. This fat soluble form of thiamine plays a very important role in the glucose metabolism. With the regular usage of Benfothiamine sensation can be restored in diabetic peripheral neuropathy.

**Niacinamide:** Has been shown to slow down the destruction of insulin-producing beta cells, enhancing their regeneration and boosting pancreatic function.

**Pyridoxine:** Vitamin B6 is essential in the reduction of Homocysteine- a byproduct of oxidation.
**Chromium:** Helps insulin to attach at the receptor site, it is the most critical mineral in the management of diabetes, the people who are deficient in chromium would have a very chance of developing insulin resistance and therefore diabetes.

**Vanadium:** Improves glucose metabolism and mimics insulin, thereby reduces the insulin release and helps control BS levels.

**Zinc:** Enhances glucose movement is stored in high quantities in beta cells and plays a very important role in the production of insulin.

**Selenium:** Is an essential mineral for glucose metabolism and critically supports the thyroid function and the metabolism.
Diabetall™ & Diabetplus™

• Unique methods of extraction (2 patents)
• Unique method of blending
• Most advanced composition of vitamins, minerals, antioxidants and herbs
• Based on the research and experience of more than 45 years

As a complimentary effect

• Normalizes the levels of total cholesterol
• Increases HDL
• Reduces LDL
• Taken over a period insulin sensitivity increases
• The amount of endogenous insulin released is reduced
• Reduces inflammation
• Reduces Oxidative stress
• Pancreas go through a process of healing and recuperation
• A sense of well being is achieved
Way to Reverse Diabetes

Insulin resistance

β-cell dysfunction

HbA1C

Diabetall™ & Diabetplus™

Exercise

Diet
Analysis of Patient data- Ground Reality

Assessment of the levels of

• HbA1C,
• Fasting Plasma Glucose
• Post prandial Glucose values in patients with Type 2 diabetes

Study Period – across the year 2013-2015
Number of patients – 600
Data available for 486 patients

• The blood sugar and HbA1C of the patients belonging to the same category followed a similar trend.
• The trends that are observed in the levels of HbA1C and blood sugar have been represented in a graphical form.
The patients were divided into 4 categories-

**GROUP 1**: ≥55 years who have recently developed Diabetes and are on OHD and our supplements along with Diet and exercise

**GROUP 2**: <55 years who have been diabetic for more than 2 years and are on OHD and our supplements along with Diet and exercise

**GROUP 3**: <55 years who have recently developed Diabetes and are not on OHD but are on our supplements along with Diet and exercise

**GROUP 4**: ≥55 years who have been diabetic for more than 10 years and are on OHD and our supplements along with Diet and exercise
Blood sugar and HbA1C trend for patients ≥55 years who have recently developed Diabetes and are on OHD and our supplements. (N=217)
Changes in lipid profile of <55 years who have been diabetic for more than 2 years and are on OHD and our supplements (N= 115)

B. Sugar Levels

Lipid Profile

- T. Cholesterol
- Triglycerides
- HDL
- LDL
- VLDL

HbA1c

B.Sugar Levels

Lipid Profile
Blood sugar and HbA1C trend for patients <55 years who have recently developed Diabetes and are not on OHD but are on our supplements. (N=45)
Blood sugar and HbA1C trend for patients ≥55 years who have been diabetic for more than 10 years and are on OHD and our supplements. (N= 109)

B. Sugar Levels

Lipid Profile

- T. Cholesterol
- Triglycerides
- HDL
- LDL
- VLDL

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</table>
Statistical data of HBA1C values (N=31) for one quarter
Statistical Data of Fasting Plasma Glucose values (N=31) for one quarter
Statistical Data of Post Prandial Plasma Glucose values (N=31) for one quarter
My name is V K Panchal from greater Noida
Improved Patient Outcomes

- Insulin resistance ↓
- Beta cell function ↑
Thank You
3. New FDA Approved Drugs


13. American Diabetic Association


24. Finegood DT & Topp B. *Diabetes Obes Metab* 2001; 3 (Suppl. 1):S20–S27