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Sanjiv J. Shah

Diabetes Action Centre
Mumbai, India

Receipt of honoraria or consultation fees: Eli Lilly, Sanofi, Astrazeneca, B1, E-Merck, USV, ERIS, Lupin. Member of a company advisory board, board of directors or other similar group: Eli Lilly, Sanofi, Astrazeneca, B1, E-Merck, USV, ERIS, Lupin
The Changing Face of Diabetes
Plan of talk

1. Newer expanded concept of Patho-physiology.
2. Brief review of newer drugs in one decade, based on patho-physiological concepts.
3. Less well known complication of Cognitive Impairment.
The Ominous Octet

- Islet β-cell: Impaired Insulin Secretion
- Islet α-cell: Increased Glucagon Secretion
- Decreased Incretin Effect
- Decreased Glucose Uptake
- Increased Lipolysis
- Increased Glucose Reabsorption
- Increased HGP
- Neurotransmitter Dysfunction
- Decreased Glucose Uptake
Development of Anti-diabetic Agents has been at a good pace...
New Dimension in managing T2DM

- Decreased Insulin Secretion
- Increased Glucagon Secretion
- Decreased Incretin Effect
- Increased Hepatic Glucose Production
- Increased Neurotransmitter Dysfunction

Adapted from De Fronzo RA. Diabetes. 2009;58:773-95.
From the triumvirate to the ominous octet: A new paradigm for the treatment of T2DM


- Increased glucagon secretion
- Increased hepatic glucose production
- Decreased insulin secretion
- Decreased incretin effect
- Increased lipolysis
- Increased glucose reabsorption
- Decreased glucose uptake
- Neurotransmitter dysfunction

- Sulphonylureas
- Meglitinides
- Alpha glucosidase Inhibitors
- Thiazolidinediones
- Metformin
- Incretin based therapies

Hyperglycaemia

SGLT 2 inhibitors
Clinical Case

- Mr. P.K., M/54 yrs,
- Type 2 Diabetes diagnosed 8 yrs back
- Treated Initially with diet + exercise for 1 yr
- Metformin was added and then gradually increased to 2000 mg/day.
- Glimepiride was added 5 yrs back, now uncontrolled, on Metformin + Glimepiride (2000mg+4mg) combination treatment.
- His weight did not change much over 8 yrs and his current weight is 80 kg and his BMI is 29.
Question

- Mr. P.K. has following reports:
  - FPG 145, PPG 220 mg/dl; HbA1c 8.5%

- Which drug should be selected to add as 3rd drug?
  - A  Basal Insulin
  - B  GLP 1 receptor agonist
  - C  DPPIV inhibitor
  - D  SGLT2 inhibitor
## Treatment options

<table>
<thead>
<tr>
<th>OPTIONS</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TZD</td>
<td>Oral, efficacy, low risk of hypoglycaemias, price</td>
<td>Edema, risk of heart failure, weight gain</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Oral, neutral weight effect, rare side effects, low risk of hypoglycaemias</td>
<td>Moderate efficacy, price</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Oral, weight loss, blood pressure reduction, low risk of hypoglycaemias</td>
<td>Moderate efficacy, genitourinary infections, price, eGFR</td>
</tr>
<tr>
<td>Insulin</td>
<td>High efficacy</td>
<td>Hypoglycaemias, weight gain, ≥1 injections/day, self-monitoring of glucose</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>High efficacy, weight loss, blood pressure reduction, low risk of hypoglycaemias</td>
<td>Gastrointestinal side effects, injectable, price</td>
</tr>
</tbody>
</table>

Note: SGLT2 Inhibitors and GLP-1 RAs are not indicated for weight loss.

## Asian Data: Sitagliptin Monotherapy Change from Baseline in HbA1c

<table>
<thead>
<tr>
<th>Country</th>
<th>Placebo Subtracted % A1c change *Baseline 8.74%</th>
<th>95% Confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>-1.36</td>
<td>(-1.73, -0.99)</td>
</tr>
<tr>
<td>China</td>
<td>-0.69</td>
<td>(-0.92, -0.46)</td>
</tr>
<tr>
<td>Korea</td>
<td>-1.38</td>
<td>(-1.92, -0.83)</td>
</tr>
</tbody>
</table>
Linagliptin Efficacy Across Ethnicities
Japanese, Asian, White

HbA1c (%) Reduction

Japanese (12 wk)  Asian (24 wk)  White (24 wk)

-0.87  -0.91  -0.52

✓ 58.2% Asians were Indian
✓ Similar trough concentrations
✓ 24-hr DPP4-inhibition >80%

Sarashina A et al. doi: 10.1111/jdi.12482
Gliptins have a promising safety profile among antidiabetics

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>GLP-1 RA</th>
<th>SGLT-2i</th>
<th>DPP-4i</th>
<th>AGi</th>
<th>TZD (moderate dose)</th>
<th>SU</th>
<th>GLN</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPO</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>GLN</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate to Severe</td>
<td>Neutral</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>Slight Loss</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Loss</td>
<td></td>
</tr>
<tr>
<td>RENAL/GU</td>
<td>Contraindicated CKD Stage 3B,4,5</td>
<td>Exenatide Not Effective with eGFR &lt; 45</td>
<td>Not Effective with Genital Mycotic Infections</td>
<td>Dose Adjustment Necessary (Except Linagliptin)</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>GI Sx</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
</tr>
<tr>
<td>CHF</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Possible Benefit</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>CARDIAC</td>
<td>Neutral</td>
<td>Benefit</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neural</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Safe</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>ASCVD</td>
<td>Benefit</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Negative Fracture Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>BONE</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Fracture Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm 2016

- Few adverse events or possible benefits
- Use with caution
- Likelihood of adverse effects
- ? Uncertain effect
Glycemic variability & microvascular complications

Daily glucose fluctuations despite near target HbA1c are implicated in microvascular complications

Patients with painful diabetic neuropathy had higher variations in daily glucose levels than painless.

Gliptins are known to reduce Glycemic variability

GV: glycemic variability; CGMS: continuous glucose monitoring system
DPP4 inhibitors: Pleiotropic effects

- Proposed cardio-protective action of GLP-1
- Proposed cyto-protective action.
- Proposed anorexic effect of GLP-1
- Proposed hepato-protective action and improvement of NASH
- Proposed maintenance of bone health
- Proposed wound healing action
- Proposed delay of diabetic nephropathy by reduction in microalbuminuria.

Gupta V. Pleiotropic effects of incretins. Indian Journal of Endocrinology and Metabolism. 2012(16); S 47-56
Groop et al. Linagliptin Lowers Albuminuria on Top of Recommended Standard Treatment in Patients With Type 2 Diabetes and Renal Dysfunction. Journal of Diabetes Investigation. 2012:3(1);105.
Linagliptin: Renal Safety and Protection Proof of Concept*

Renal Safety: Pooled Analysis of 13 RCTs¹

N = 5466 (Linagliptin: 3505; Placebo: 1961)

**Incidence Rate of Renal Events**

- **Placebo**: 311.7 per 1000 Person Years
- **Linagliptin**: 268.4 per 1000 Person Years

HR: 0.84 (95% CI 0.72 - 0.97)  
P = 0.02

*This is a proof of concept from retrospective analyses of 13 trials. Confirmatory CARMELINA trial is underway*

GLP-1 or GLP-1R agonists lead to increased insulin sensitivity, which in turn affects various bodily functions:

- **Brain**: Decreased appetite, increased satiety, increased energy expenditure
- **Heart**: Decreased blood pressure, increased heart rate, increased myocardial contractility, increased cardioprotection
- **Kidney**: Increased natriuresis
- **Liver**: Decreased hepatic glucose production
- **Adipose tissue**: Increased lipolysis, increased FFA synthesis, increased glucose uptake
- **Muscle**: Increased glycogen synthesis, increased glucose oxidation

In addition, GLP-1 and GLP-1R agonists affect:

- **GIT**: Decreased gastric emptying, increased acid secretion, increased GI motility
- **Pancreas**: Increased insulin secretion, decreased glucagon secretion, increased insulin biosynthesis, increased β-cell survival, increased β-cell proliferation
## Characterization of various GLP1-RA

<table>
<thead>
<tr>
<th>GLP1-RA</th>
<th>Half-life</th>
<th>Dosing</th>
<th>Titration</th>
<th>Injection meal related</th>
<th>Duration of Action</th>
<th>Reconstitution required? Extra action for device…</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lixisenatide¹,²</td>
<td>3 hours</td>
<td>Once daily</td>
<td>yes</td>
<td>yes</td>
<td>Short</td>
<td>no</td>
</tr>
<tr>
<td>Exenatide BID⁴</td>
<td>2-4 hours</td>
<td>Twice daily</td>
<td>yes</td>
<td>yes</td>
<td>Short</td>
<td>no</td>
</tr>
<tr>
<td>Liraglutide³</td>
<td>13 hours</td>
<td>Once daily</td>
<td>Yes</td>
<td>no</td>
<td>Intermed.</td>
<td>no</td>
</tr>
<tr>
<td>Exenatide QW⁵,⁶</td>
<td>2 weeks</td>
<td>Once weekly</td>
<td>no</td>
<td>no</td>
<td>Long</td>
<td>yes</td>
</tr>
<tr>
<td>Albiglutide⁷,⁸</td>
<td>6–8 days</td>
<td>Once weekly</td>
<td>yes</td>
<td>no</td>
<td>Long</td>
<td>yes</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>4-5 days</td>
<td>Once weekly</td>
<td>No?/ tbd</td>
<td>no</td>
<td>Long</td>
<td>No (invisible needle)</td>
</tr>
</tbody>
</table>

Change in HbA1c:
Once weekly GLP-1RA vs other Injectable therapies

[Diagram showing study results and comparisons]

NOTE: Weights are from random effects analysis

Karagiannis T et al., DOM 2015
Pleiotropic effects of GLP-1

GLP-1 RAs
Safety Issues

- Pancreatitis
  - 2014 FDA and EMA stated, "Assertions of a causal association are not consistent with current data" and continue to investigate the safety of these drugs\(^a\)
  - All patients with diabetes have 1.84-3 times increased risk of acute pancreatitis\(^b,c\)
  - Educate patients to be aware of symptoms
- Do not use if personal or family history of medullary thyroid cancer or MEN2\(^d-h\)
- Use agents with caution in patients with renal impairment\(^d-h\)
- Hypovolemia can result from nausea and vomiting\(^d-h\)

Diabetes and cancer exhibit similar pathophysiology

- Obesity, insulin resistance, chronic inflammation, oxidative stress and unbalance of adipokines are common pathophysiological backgrounds of diabetes and cancer.

✓ Amongs all anti-diabetics metformin, thiazolidinediones and GLP1 agonists, have been reported to reduce cancer risk and progression.

SGLT2 inhibitors

Dapagliflozin, Canagliflozin, Empagliflozin
HbA1c Outcomes in Patients Treated With Canagliflozin Versus Sitagliptin in a US Health Plan

Sarah W. Thayer, MA; Richard Aguilar, MD; Wing Chow, PharmD, MPH

©Optum, Eden Prairie, MN; ©Diabetes Nation LLC, Sisters, OR; ©Janssen Scientific Affairs, LLC, Raritan, NJ.

CANA had a greater reduction in HbA1c with more patients achieved HbA1c goals than SITA

Poster presented at ADA 2016 Scientific Sessions
SGLT2 Inhibitors for Treatment of Type 2 Diabetes

SGLT2 inhibitors block reabsorption of filtered glucose in kidneys — leads to glucosuria, improved glycemic control

**Benefits**
- Insulin-independent action
- Associated with caloric loss; could result in weight loss
- Low hypoglycemia
- Complement action of other antidiabetic agents
- Can be used regardless of diabetes duration

**Side effects**
- Repeated urinary tract infections
- Genital infections
- Increased hematocrit
- Decreased blood pressure

One formulation of the SGLT2 inhibitor canagliflozin (SGLT2=sodium-glucose co-transporter 2) has been FDA approved as of May 2013.

Canagliflozin: Significant Weight Reduction as monotherapy or in combination with OADs/Insulin

Add-on combinations with

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>BL Mean Weight (kg)</th>
<th>Placebo-subtracted LS Mean</th>
<th>% Change in Body Weight (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy (DIA3005)</td>
<td>584</td>
<td>86.8</td>
<td>-2.2*</td>
<td>-2.2% (CI -3.3, -1.3)</td>
</tr>
<tr>
<td>Metformin (DIA3006)</td>
<td>1284</td>
<td>87.2</td>
<td>-2.5*</td>
<td>-2.5% (CI -2.9, -2.1)</td>
</tr>
<tr>
<td>SU (DIA3008)</td>
<td>127</td>
<td>83.0</td>
<td>-2.9*</td>
<td>-2.9% (CI -3.3, -2.6)</td>
</tr>
<tr>
<td>Met/SU (DIA3002)</td>
<td>469</td>
<td>92.8</td>
<td>-1.4*</td>
<td>-1.4% (CI -1.8, -1.0)</td>
</tr>
<tr>
<td>Met/Pio (DIA3012)</td>
<td>342</td>
<td>94.1</td>
<td>-2.0*</td>
<td>-2.0% (CI -2.4, -1.6)</td>
</tr>
<tr>
<td>Insulin (DIA3008)</td>
<td>1718</td>
<td>97.0</td>
<td>-1.9*</td>
<td>-1.9% (CI -2.4, -1.4)</td>
</tr>
<tr>
<td>Current Therapy in Older Subjects (DIA3010)</td>
<td>714</td>
<td>89.5</td>
<td>-2.3*</td>
<td>-2.3% (CI -2.8, -1.8)</td>
</tr>
</tbody>
</table>

*C p <0.001; † p <0.05

* Based on ANCOVA models, data prior to rescue (LOCF)

**References**

Forst T et al. Poster presented at the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy), 2012;Nov.8-11; Barcelona, Spain, (P64).
Wilding J et al. Poster presented at the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy), 2012;Nov.8-11; Barcelona, Spain, (P73).
Blood Pressure Effects of SGLT2 Inhibitors

Additional 3-6 mm Hg reduction in systolic blood pressure

- No clear relationship between blood pressure decreases and weight loss
- Osmotic diuretic-like effect?

The diastolic blood pressure, likewise, drops between 2-3 mm Hg.

The BP effects are thought to be related to the osmotic diuretic effect and very mild natriuresis. SGLT2 Inhibitors may affect nitric oxide, and it is currently under investigation.

**Summary of completed T2D CVOTs for newer T2D agents**

<table>
<thead>
<tr>
<th>Study</th>
<th>Condition/Endpoints</th>
<th>Primary endpoint</th>
<th>Hazard ratio</th>
<th>Randomisation</th>
<th>Median follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI 53¹</td>
<td>CVD or CRFs, HbA₁c 6.5–12.0% n = 16,492</td>
<td>Saxagliptin vs Placebo</td>
<td>Primary endpoint 3P-MACE</td>
<td>2.1 year median follow-up</td>
<td>1.00 (95% CI 0.89–1.12) Non-inferior</td>
</tr>
<tr>
<td>EXAMINE²</td>
<td>ACS, HbA₁c 6.5–11.0% n = 5380</td>
<td>Alogliptin vs Placebo</td>
<td>Primary endpoint 3P-MACE</td>
<td>1.5 year median follow-up</td>
<td>0.96 (upper CI* 1.16) Non-inferior</td>
</tr>
<tr>
<td>TECOS³</td>
<td>CVD, HbA₁c 6.5–8.0% n = 14,735</td>
<td>Sitagliptin vs Placebo</td>
<td>Primary endpoint 4P-MACE</td>
<td>3.0 year median follow-up</td>
<td>0.98 (95% CI 0.88–1.09) Non-inferior</td>
</tr>
<tr>
<td>ELIXA⁴</td>
<td>ACS, HbA₁c 5.5–11% n = 6068</td>
<td>Lixisenatide vs Placebo</td>
<td>Primary endpoint 4P-MACE</td>
<td>2.1 year median follow-up</td>
<td>1.02 (95% CI 0.89–1.17) Non-inferior</td>
</tr>
</tbody>
</table>

*Upper boundary of 1-sided repeated CI.

CV Outcomes with Empagliflozin

NEJM; 2015
“Empagliflozin is the first of the recently approved diabetes treatments associated with a lower risk of cardiovascular disease.”

CV death and lower risk of hospitalization for heart failure
Empagliflozin protects kidney function

**eGFR over time**

![Graph showing eGFR over time with adjusted mean (SE) eGFR values for different doses of Empagliflozin and Placebo.]

Mixed model repeated measures analysis in the treated set (OC-AD)
Studies of Metformin + DPP-4i + SGLT2 Inhibitors Combination Therapy

Separate Studies & Not Direct Comparisons

<table>
<thead>
<tr>
<th>Add-on to</th>
<th>Add-on to Metformin XR</th>
<th>Add-on to Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin+Sitagliptin (24 weeks) BL ~ 7.9%</td>
<td>DAPA 10 + SAXA 5</td>
<td>EMPA 25/LINA 5 FDC</td>
</tr>
<tr>
<td>DAPA 10</td>
<td>n=158</td>
<td>n=134</td>
</tr>
<tr>
<td>PBO</td>
<td>n=151</td>
<td>n=135</td>
</tr>
<tr>
<td>n=224 (n=223)</td>
<td>n=143</td>
<td>n=140</td>
</tr>
<tr>
<td>-0.5*</td>
<td>-1.20</td>
<td>-0.62</td>
</tr>
<tr>
<td>*p&lt;0.001 vs PBO</td>
<td>*superior to DAPA 10 (p&lt;0.02)</td>
<td>*superior to EMPA 25 (p&lt;0.001)</td>
</tr>
<tr>
<td>(No statistical comparison between DAPA 10 and SASSA 5)</td>
<td>† superior to SASSA 5 (p&lt;0.0001)</td>
<td>† superior to EMPA 10 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(No statistical comparison between EMPA 10 or 25 and LINA 5)</td>
</tr>
</tbody>
</table>

| Δ in Wt (kg): | -2.4* | -2.1* | -3.0* |
| Δ in SBP (mmHg): | -2.4 | 0 | -2.6* |
| | ND | ND | -3.2 |
| | ND | -1.9 | -3.6* |
| | | -3.5 | -2.8* |
| | | +0.3 | -2.8 |


Triple therapy with Metformin/DPP-4i/SGLT2i is not approved in Canada
FDC EMPA/LINA is not approved for use in Canada.
Incretin+Metformin+SGLT2i

- GLP-1 receptor agonists, and DPP-4 inhibitor treatment, and metformin and SGLT-2 inhibitor treatment are 3 distinct strategies.
- The true aim of glycemic control is the prevention of complications such as cardiovascular events and cancers.
- In addition, the anticancer effect of SGLT-2 inhibitor could be expected from experimental data and its effect on reducing both body weight and serum insulin level.
- The anticancer effects of metformin are well known. The reduction of cardiovascular events by metformin has been reported.
- We speculate that the anticancer and vascular protective effects of incretin therapy will be reported more in the near future.

Cognitive Impairment in Diabetes

• A challenging problem in a growing geriatric population.

• Recent studies have shown a link between T2DM and mild cognitive impairment (CI), Alzheimer's disease, and vascular dementia.

• 7-year follow-up study of 1 million subjects in Taiwan, Among the parameters studied, female gender, older age, insulin use, and previous episodes of hypoglycemia were at high risk for dementia.

Cognition and Cognitive Impairment

• Cognition is defined as “the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses”

• Changes in memory, mood swings, perception, reaction times, attention, and concentration.
Cognitive Impairment in Diabetes

Hyperglycemia

- Glycation, oxidative stress, endothelial dysfunction, increased activity of polyol pathway

Hypertension

Macroangiopathy (cerebrovascular disease)

- Insulin resistance
- Abnormal insulin action
- Insulin deficiency

Microangiopathy

COGNITIVE IMPAIRMENT

- Vascular dementia
- Alzheimer's disease

Hyperglycemia

- Younger
- Older

Aging

Depression

Genetic factors

Daily habits
- Smoking
- Diet
- Stress
- Exercise
Pathophysiology of Cognitive Impairment

Multifactorial:

1. A strong link between lack of glycemic control and glycemic variability resulting in hypo-or hyperglycemia.

2. Repeated short-term hypoglycemic states may result in permanent brain damage.

3. Micro- and macrovascular changes associated with T2DM are also linked to the development of dementia.

4. Increase in inflammatory cytokines.

5. Brain changes are similar to amylin deposition in beta cells.
Brain imaging using MRI of patients with hyperglycemia for long periods of time can show visible lesions of neuronal damage as microstructural damage in cerebral gray and white matter.

A decrease in white matter volume has been linked to loss of cognitive function.

Clinical Assessment:

- Mini-Mental State Examination (MMSE)
- Addenbrooke's Cognitive Examination-Revised (ACE-R)

Treatment or Prevention of Cognitive Impairment

- Better glycemic control
- SMBG to prevent hypoglycemia
- Use op PPAR agonist like Pio or Rosi-glitazone.
- Use of GLP1 agonist.
- Clear written instructions of care
Fracture Risk in Diabetes

• Hip fracture risk is increased, at an age-adjusted relative risk of 1.4, if adjusted for BMI and BMD, RR is 1.7.

• Frequent falls are one possible explanation for this higher fracture risk at a given BMD.

• The relative risk of falling is 1.2 for patients with T2DM.

• In ACCORD trial, compared with standard glycemic control, intensive glycemic control did not increase or decrease fracture or fall risk.

• Fracture risk (Fracture Risk Assessment Tool-FRAX) is increased with A1C> 8%.
The mechanisms underlying low bone strength in diabetes

- Type 1 diabetes mellitus affects the skeleton more severely than T2DM, probably because of the lack of the bone anabolic actions of insulin and other pancreatic hormones.
- Impact of nephropathy on peak bone mass.
- Bone mass can remain high in patients with T2DM, but it does not protect against fractures, as **bone quality** is impaired.
- The class of antidiabetic glitazones drugs can promote bone loss and osteoporotic fractures in postmenopausal women, therefore, avoid if osteoporosis is diagnosed.
Mechanism of Bone Loss

Bone, sweet bone - Osteoporotic fractures in diabetes mellitus
Nature Reviews Endocrinology 2012 ·
Diabetic bone fragility is characterized by:

- More rapid bone loss
- Smaller cross-sectional area of bone
- Worse trabecular bone score
- Reduced bone formation
- Cortical porosity
- Higher marrow fat
- Less resistance to microindentation
- Advanced glycation endproducts (AGEs)
- Possible microvascular damage in bone
Metformin increases the differentiation of MSCs into osteoblasts through its actions on RUNX2. Glitazones simultaneously suppress RUNX2 and activate PPARγ, which drives differentiation of MSCs into adipocytes, thereby reducing osteogenesis.
Expectation from a Clinician

• Increased awareness of osteoporosis is needed in view of the growing and aging population of diabetes patients.
• Assessment of BMD and other risk factors as part of the diagnostic procedure.
• A physically active, healthy lifestyle and prevention of diabetic complications, along with calcium and vitamin D repletion.
• All osteoporosis drugs seem to be effective in patients with diabetes mellitus.
Thank You

Every piece of information helps