# Is Alzheimer's disease - type 3 diabetes?

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## Summary

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Two types' diabetes mellitus and diabetes insipidus are reported so far. The present review states the various aspects of diabetes and Alzheimer's disease as well as their common pathophysiological processes, the role of amyloid precursor protein, neurofibrillary tangles, similarities and the possibilities of the Alzheimer's disease to become type 3 diabetes. The present review also shows the possible future treatment for this disease.

**Keywords:** Diabetes, Alzheimer's disease, amyloid protein,

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## Introduction

Diabetes generally refers to Diabetes Mellitus or, less often, to Diabetes Insipidus. Diabetes Mellitus and Diabetes Insipidus share the name "Diabetes" because they both conditions are characterized by excessive urination (polyuria). **[1]**

**Fig.1 Universal Blue Circle Symbol for Diabetes**

The word "Diabetes" is borrowed from the Greek word meaning "**a siphon.**" The 2nd-century A.D. Greek physician, **Aretus** the **Cappadocian**, named the condition "Diabetes." He explained that patients with it had polyuria and "passed water like a siphon." When "diabetes" is used alone, it refers to Diabetes Mellitus. **[2, 3]**

**Diabetes mellitus**

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. **[4]**

**1. Type 1 Diabetes:-** Autoimmune destruction of insulin-producing cells leading to hyperglycemia (high blood glucose).

**2. Type 2 Diabetes: -** Insulin resistance leading to hyperglycemia (high blood glucose).

**3. Type 3 Diabetes: -** Depletion of insulin in the brain leading to Alzheimer's disease.

**4. Type 4 Diabetes: -** Elevated insulin levels leading to hypoglycemia (low blood glucose), chronic pain and related complications.

**5. Other Types: -** Gestational Diabetes **–** Pregnancy induced Diabetes.

Type 1 and Type 2 diabetes are recognized medical terms. Type 3 Diabetes is a new term proposed by a research team at Brown Medical School. Type 4 Diabetes is new term for malfunctioning blood glucose control leading to low blood sugar and Neuropathic complications. **[5]**

**Diabetes Insipidus**

Diabetes Insipidus (DI) is a disorder in which there is an abnormal increase in diluted urine output, fluid intake and often thirst. Diabetes Insipidus is not the same as diabetes mellitus ("sugar" diabetes). Diabetes Insipidus resembles diabetes mellitus because the symptoms of both diseases are increased urination and thirst. However, in every other respect, including the causes and treatment of the disorders, the diseases are completely unrelated. Sometimes Diabetes Insipidus is referred to as "water" diabetes to distinguish it from the more common diabetes mellitus or "sugar" diabetes. **[6]**

**1. Neurogenic Diabetes Insipidus**

Neurogenic diabetes insipidus, more commonly known as central diabetes insipidus, is due to a lack of arginine vasopressin (AVP), also known as antidiuretic hormone (ADH) production in the brain.

**2. Nephroenic Diabetes Insipidus :-**Nephrogenic diabetes insipidus is due to the inability of the kidney to respond normally to ADH.

**3. Dipsogenic Diabetes Insipidus :-**Dipsogenic DI is due to a defect or damage to the thirst mechanism, which is located in the hypothalamus. This defect results in an abnormal increase in thirst and fluid intake that suppresses ADH secretion and increases urine output.

**4. Gestational Diabetes Insipidus :-** Gestational DI only occurs during pregnancy. While all pregnant women produce vasopressinase in the placenta, which breaks down ADH, this can assume extreme forms in Gestational DI **[7, 8, 9]**

**Symptoms**

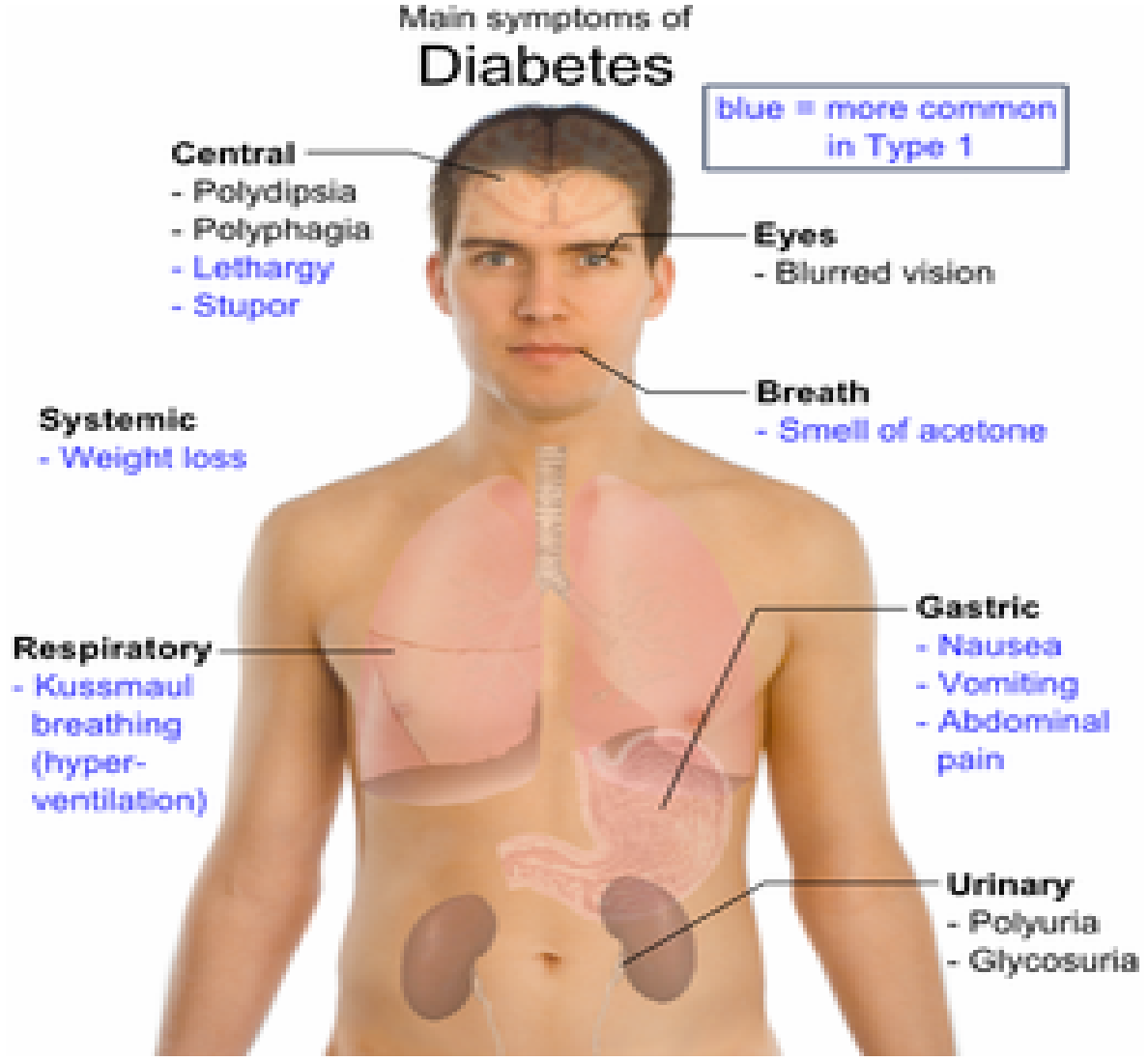



**Fig 2 Main symptoms of diabetes**

**Pathophysiology**

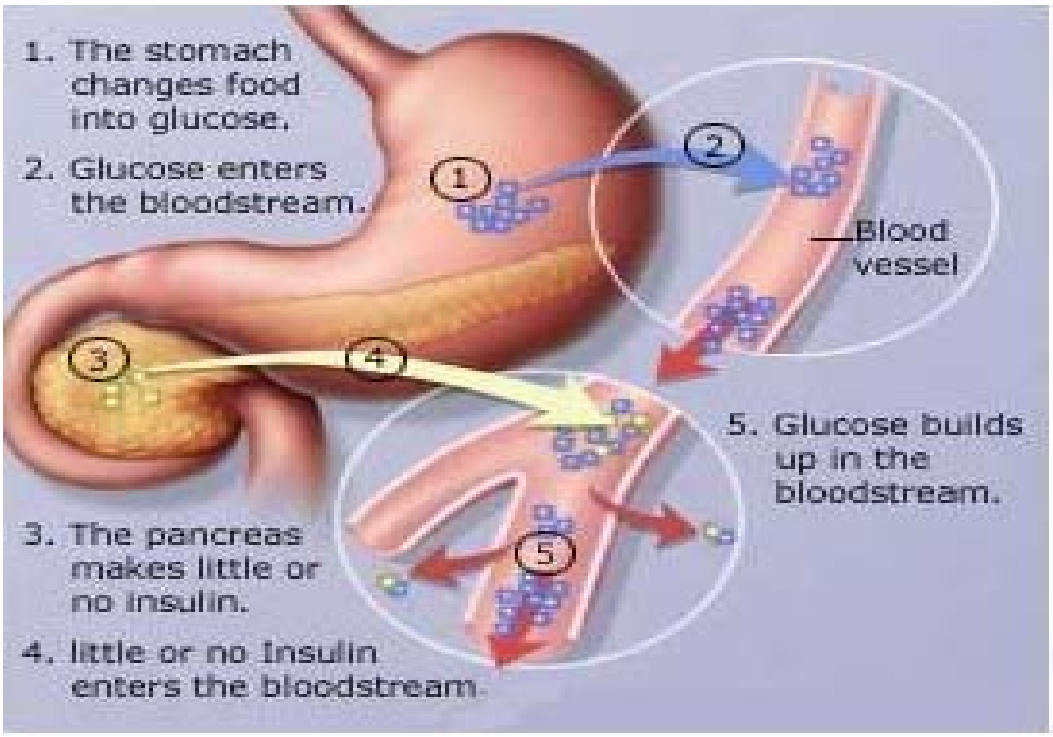



**Fig. 3 Pathophysiology of diabetes**

**Alzheimer's disease**

Alzheimer's disease is a brain disorder named for German physician Alois Alzheimer, who first described it in 1906. Number of patients of Alzheimer in 2006 was 26.6 million worldwide.

**Symptoms [10]**

1. Memory changes that disrupt daily life.
2. Challenges in planning or solving problems.
3. Difficulty completing familiar tasks at home, at work or at leisure.
4. Confusion with time or place.
5. Trouble understanding visual images and spatial relationships.
6. New problems with words in speaking or writing.
7. Misplacing things and losing the ability to retrace steps.
8. Decreased or poor judgment.
9. Withdrawal from work or social activities.
10. Changes in mood and personality.

**Pathopysiology [11]**

**1. Amyloid precursor protein**

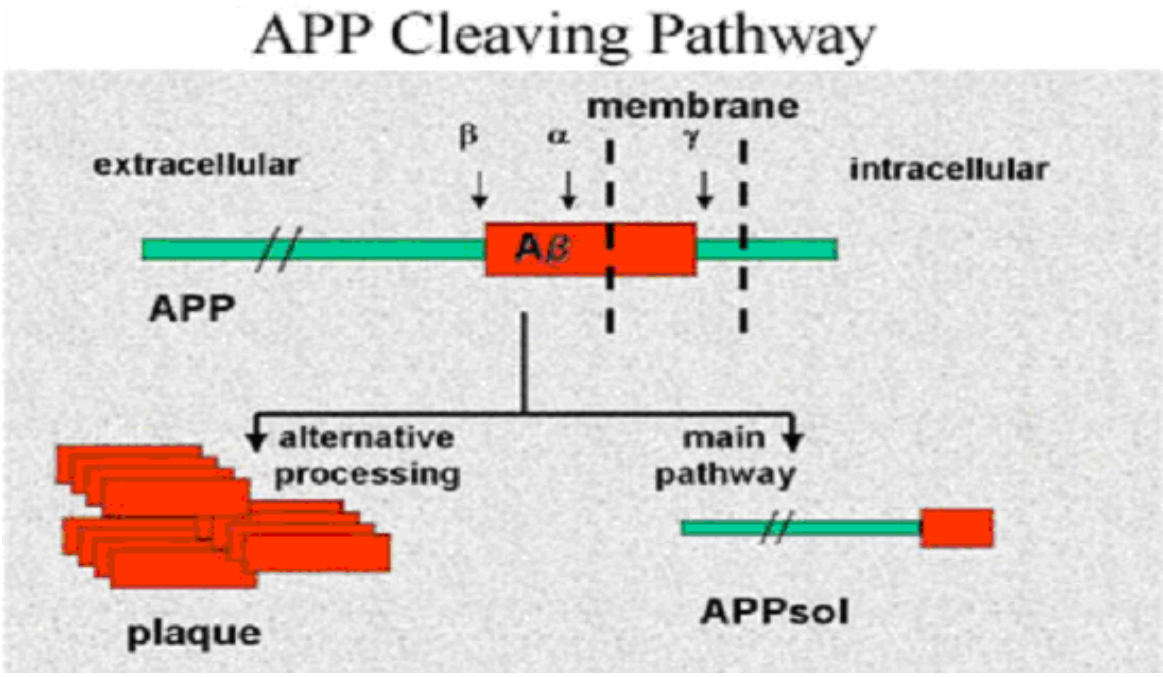



**Fig. 4 Amyloid Precursor Protein**

**2. _Neuro Fibrillary Tangles :-**

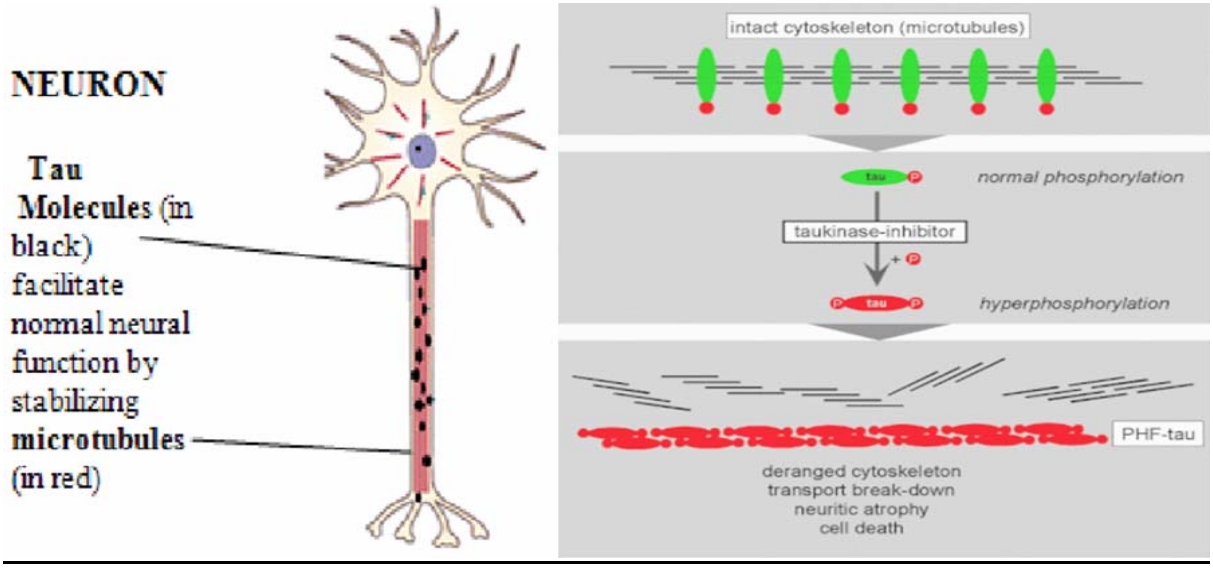
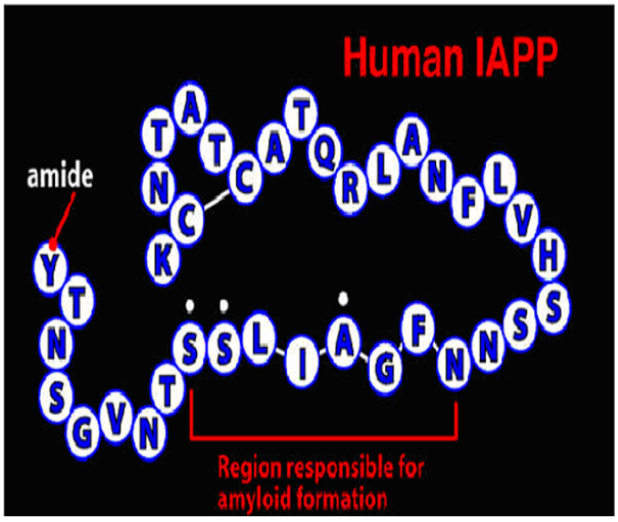



**Fig. 5 Neuro Fibrillary Tangles**

**Common Pathological Processes Between Alzheimer's disease & Type 2 diabetes [12]**



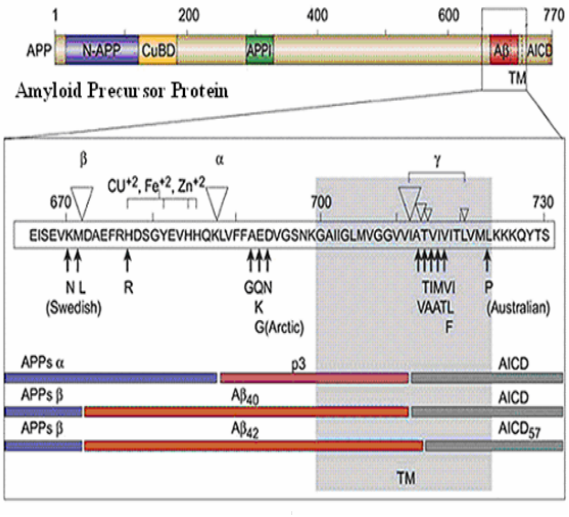




**Fig. 6 Diabetes [13]** **Fig. 7 Alzheimer's disease [14]**

APP & IAPP are 90% similar in structure. Due to point mutation β & γ-secretes activity is more than α-secretes (see Fig.13,14).

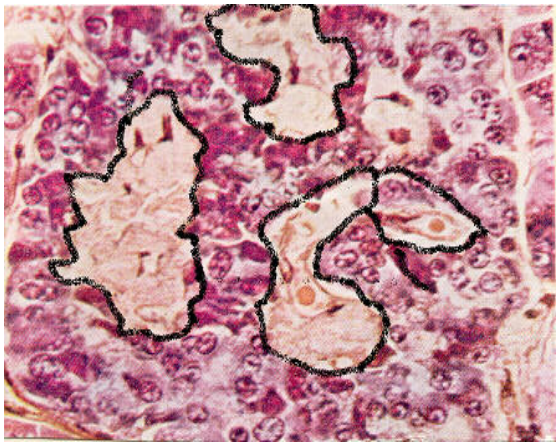


**Fig. 8 Amyloid highlighted in islets**

Amyloid highlighted within a single islet(see Fig.8) Amylin Derived Islet Amyloid forms between beta cells and between beta cells and endothelial cells creating a diffusion barrier (space occupying lesion) resulting in a secretory defect and an absorptive defect surrounding islet capillaries.

- **Neuro fibrillary tangles**

Tau phosphorylation in Alzheimer's disease and Type 2 Diabetes Mellitus involves Glycogen Synthase Kinase-3 activation, a Serine / Threonine Kinase that Phosphorylates Glycogen Synthase, in the rate limiting step of glycogen biosynthesis.

- **Insulin**

Insulin resistance occurs in CNS due to alteration in Insulin Receptor sensitivity. Researchers have found that in Mammalians Insulin is produced in Pyramidal cells of brain.

**Functions:** - Act as Neuromodulater,
- Improve learning and memory power,
- Regulate Body Energy Homeostasis
- In Synaptic Plasticity.

- **Advanced Glycation End Products**

**Diabetes Mellitus**

Normally AGEs formed due to Non enzymatic reaction of Glucose-Protein condensation and also occur with Lipids and Nucleic acids. In DM, above reaction occurs at faster rate because there is more glucose present.

**Alzheimer's disease**

Increase accumulation of Amyloid-β plaques by Amyloid-β Glycation. Increase Hyperphosphorylation of Tau by Glycation of Tau Protein.

- **Transforming Growth Factor-β**

It plays an important role in Tissue Regeneration, Cell Differentiation, and Embryonic development, Regulate Immune system and Apoptosis, in inflammatory diseases.

**Diabetes Mellitus:** Increase plasma TGF-β1 level.

**Brain:** - TGF-β expression is reduced.
- TGFβ1 dissolves Amyloid-β plaques.
- TGFβ2 dissolves NeuroFibrillary Tangles.

- **Evidence From Animal Models**

Streptozotocin in brain impairs glucose and energy metabolism, Learning, memory formation, decrease choline acetyltransferase. Hence, this is a novel model of Alzheimer's disease.

After giving intracerebrovascular Streptozotocin animal shows brain lesions, Reduction in size of Brain,neurodegeneration with cell loss, increase Tau phosphorylation & Amyloid β level, increase GSK3-β activity, oxidative stress in brain, impair learning over 3 months.

**Future Treatments**

These Drugs are in the Phase 3 of Clinical Trial **[15]**

| No. | Name of Drug | Mechanism of action |
|---|---|---|
| 1 | α-Tocopherol | Prevent brain cell damage by Destroying Toxic Free Radicals. |
| 2 | Bapineuzumab & Solanezumab | Bind & Remove Amyloid-β peptide that accumulates in Brain. |
| 3 | Cerebrolysin | Decrease Amyloid-β production & Neuroprotection in Brain. |
| 4 | Ibuprofen | Decrease Inflammation in Brain by Inhibiting COX in Brain. |
| 5 | IV Immunoglobulin | Natural Antiamyloid Antibody reduce CNS & Peripheral Amyloid-β & Improve cognition. |

| | | |
|---|---|---|
| 6 | Leuprolide | Improve cognition mainly in women. |
| 7 | Hydroxyvaleryl monobenzocaprolactam | γ -Secretase Inhibitor. |
| 8 | Valproate | Potential therapy for Agitation in Alzheimer patient. |

**Insulin sensitizers**

Recent studies suggest an association between insulin resistance and AD (sensitivity to insulin can decline with aging): In clinical trials, a certain insulin sensitizer called "Rosiglitazone" improved cognition in a subset of AD patients; it vitro, beneficial effects of Rosiglitazone on primary cortical rat neurons have been demonstrated. **[16, 17]**

**Prevention**

- Apple juice.**[18]**
- Indian Curry (Curcumin). **[19]**
- A 21-year study found that coffee drinkers of 3-5 cups day at midlife had a 65% reduction in risk of dementia/Alzheimer's disease (AD) in late-life.
- People who engage in intellectual activities such as reading, playing board games & chess, completing crossword puzzles, playing musical instruments or regular social interaction show delayed onset or reduced severity of Alzheimer's disease. Bilingualism is also related to a later onset of Alzheimer's.

## Conclusion

Alzheimer's disease cannot be called as type 3 diabetes because Studies done so far are on the preliminary basis. Similarities between both disease here discussed are only on the molecular and biochemical basis. So more study needed in future including other aspects to prove Alzheimer's disease as type 3 diabetes.

## References

**1.** International Diabetes Federation. 17 March 2006. http://www.diabetesbluecircle.org.

**2.** Kinori Kosaka. "History and of activities of Japan Diabetes Society", *Diabetes Research and Clinical Practice,* Volume 24, Supplement 1, October 1994, Pages S321- S324.

**3.** IOS Press (2009, January 24). "Apple Juice Can Delay Onset Of Alzheimer's Disease, Study Suggests". *ScienceDaily*. Retrieved December 19, 2009, from http://www.sciencedaily.com/releases/2009/01/090122100826.htm

**4.** Takeshi Kuzuya, Shoichi Nakagawa, Jo Satoh, Yasunori Kanazawa, Yasuhiko Iwamoto, Masashi Kobayashi, Kisihio Nanjo, Akira Sasaki, Yutaka Seino, Chikako Ito, Kenji Shima, Kyohei Nonaka, Takashi Kadowaki. "Report of the Committee on the classification and diagnostic criteria of diabetes mellitus", ***Diabetes Research and Clinical Practice***, Volume 55, Issue 1, January 2002, Pages 65-85.

**5.** Bob Ranson, "Introduction", ***Type 4 Diabetes :- Elevated Insulin, Lower Blood Sugar & 24/7 pain***. Published by BBG Media. Edition-2007, Pages 4-5.

**6.** Jane H. Christensen, Søren Rittig. "Familial Neurohypophyseal Diabetes Insipidus An Update", ***Seminars in Nephrology***, Volume 26, Issue 3, May 2006, Pages 209- 223.

**7.** Stephen Ball. "Diabetes Insipidus", ***Medicine***, Volume 33, Issue 11, 1 November, 2005, Pages 18-19.

**8.** Stephen Ball. "Diabetes insipidus", ***Medicine***, Volume 37, Issue 8, August 2009,Pages 414-415.

**9.** Gary L. Robertson., the Diabetes Insipidus Foundation. Available at:- http://www.diabetesinsipidus.org/whatisdi.htm Revised December, 2006.

**10.** http://www.alz.org/alzheimers_disease_10_signs_of_alzheimers.asp

**11.** www.clas.ufl.edu/jur/200308/images/patel_1.jpg

**12.** Lin Li, Christian Hölscher. "Common pathological processes in Alzheimer disease and type 2 diabetes: A review", ***Brain Research Reviews***, Volume 56, Issue 2, December 2007, Pages 384-402.

**13.** www.joplink.net/prev/200507/02_fig1.jpg

**14.** www.bath.ac.uk/biosci/images/profiles/Amyloid_Precursor_Protein.png

**15.** Bertram L, McQueen M, Mullin K, Blacker D, Tanzi R. The AlzGene, Database.Alzheimer Research Forum. Available at: http://www.alzgene.org. Revised 23 June 2005.

**16.** Richard C. Mohs, Claudia Kawas, Maria C. Carrillo. "Optimal design of clinical trials for drugs designed to slow the course of Alzheimer's disease", ***Alzheimer's and Dementia***, Volume 2, Issue 3, July2006, Pages 131-139.

**17.** Lon S. Schneider, Mary Sano. "Current Alzheimer's disease clinical trials: Methods and placebo outcomes", ***Alzheimer's and Dementia***, Volume 5, Issue 5,September2009, Pages 388-397.

**18.** IOS Press (2009, January 24). "Apple Juice Can Delay Onset of Alzheimer's disease, Study Suggests". ***ScienceDaily***. Retrieved December 19, 2009, from http://www.sciencedaily.com/releases/2009/01/090122100826.htm

**19.** Annual Meeting of the Royal College of Psychiatrists, BT Convention Centre, Liverpool, 2 -5 June 2009. Available at: http://www.medicalnewstoday.com/articles/152768.php