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CONTENTS

Editorial

PRECISION MEDICINE: NEED OF THE TIME

JK Panda[1], SK Dhar[2]

Precision Medicine is a treatment option tailored to groups of patients based on laboratory results that show predictive biomarkers (which indicate who is likely to benefit from the drug) or to individuals based on their unique genetic profile or status, such as age and gender.2

At the core of Precision Medicine is Pharmacogenomics (PGx), the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup.3

This emphasis on biomarkers – measurable substances in the body whose presence is indicative of phenomena such as disease, infection or environmental exposure – is a far different approach to the traditional "one-size-fits-all" model of designing drugs for the "average" patient.4 Tested on broad populations and prescribed using statistical averages, these conventional pharmaceuticals work for some patients but not others, due to genetic differences. This has led to a situation in which any given prescription drug now on the market works for only about half the patients who take it.1

Precision medicine, on the other hand, incorporates patient-specific information and biomarkers to help inform decisions as to optimal treatment for complex disease states. With this approach, physicians can identify patients susceptible to adverse effects; be aware of dangerous drug-drug, drug-gene and drug-drug-gene interactions; and provide care in a whole new way that is completely individualized.

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Drug-drug interactions, of course, are widely recognized, but the other two newly described interactions may be less so. In that regard, a drug-gene interaction occurs when a patient's genetic CYP450 type (e.g., CYP2D6 poor metabolizer) affects that patient's ability to clear a drug. A drug-drug-gene interaction occurs when the patient's CYP450 genotype and another drug in the patient's regimen (e.g., a CYP2D6 inhibitor) affect that individual's ability to clear a drug.

Precision medicine also is seen as a significant tool in reducing emergency hospitalizations or avoidable readmissions. A case in point: Of the five medications that most often cause emergency hospitalization due to adverse drug events, science has shown that genetic implications in an individual's metabolism influence the safety and efficacy of four.

Incorporating this key biological data with the social and behavioral aspects of a patient is anticipated to play a major role in proactive and preventative care, further improving health and reducing costs. In addition, laboratory testing can play a role in drug development by helping identify potential candidates for clinical trials.

This Precision Medicine Initiative put impetus behind the concept of personalized medications, foreseen as powerful tools for achieving drug efficacy while avoiding adverse drug events and reducing healthcare costs through prevention of drug-related hospitalizations.

While the promise of precision medicine is monumental, delivery is not without stumbling blocks and a great deal of change and effort will be required by all stakeholders. Personalized medicines accounted for nearly one of every four FDA approvals from 2014 to 2016, and the PMC estimates that more than 70 percent of cancer drugs now in development are personalized medicines. More than 250 prescription

medication labels now include information from the FDA for people with certain genetic variations. Despite its myriad and concomitant challenges, the concept of precision medicine will only get more exciting as science and technology continue to advance.

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Original Article

ASSESSMENT OF VITAMIN D STATUS IN PREDIABETICS AND NEWLY DIAGNOSED TYPE 2 DIABETIC PATIENTS.

B. Mukherjee

ABSTRACT :

Introduction : Interest in vitamin D, the so-called "sunshine vitamin," has occurred recently because it has been linked to everything from cancer and heart disease to diabetes. Research studies continue to pour into the literature stating that vitamin D is a superstar when it comes to health. In recent years, researchers have linked low vitamin D levels to insulin resistance and diabetes. Overcoming insulin resistance, in particular, could be a way to head off type 2 diabetes mellitus before it sets in.

Objective : This study was conducted to assess the vitamin D status in prediabetics and newly diagnosed type 2 diabetic patients and correlate with other physical parameters.

Materials and methods : 30 prediabetic subjects and 30 newly diagnosed adult diabetic patients attending OPD of Hi-tech Medical College, Rourkela were selected for the study. 40 normal healthy individuals were selected randomly as control. Vitamin D, FPG and HbA1c were measured along with physical parameters.

Results : Vitamin D levels were significantly lower in both prediabetics and diabetics when compared to normal subjects. There was significant correlation of vitamin D with BMI in both the study groups.

Conclusion : There is a strong inverse association between low levels of vitamin D and diabetes prevalence and supplementation with vitamin D in prediabetics may delay the progression to DM type II.

Keywords : Vitamin D; prediabetes; diabetes.

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INTRODUCTION : Vitamin D, also described as "the Sun Vitamin" is a steroid with hormone like activity. It regulates the functions of over 200 genes and is essential for growth and development. There are two forms of vitamin D. Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol).[1] Vitamin D status depends on the production of vitamin D 3 in the skin under the influence of ultraviolet radiation from sun and vitamin D intake through diet or vitamin D supplements. Usually 50 to 90% of vitamin D is produced by sunshine exposure of skin and the remainder comes from the diet. Natural diet, most human consume, contain little vitamin D. Traditionally the human vitamin D system begins in the skin, not in the mouth. However, important sources of vitamin D are egg yolk, fatty fish, fortified dairy products and beef liver. [2]

Vitamin D3 deficiency can result in obesity, diabetes, hypertension, depression, fibromyalgia, chronic fatigue syndrome, osteoporosis and neuro-degenerative diseases including Alzheimer's disease. Vitamin D deficiency may even contribute to the development of cancers, especially breast, prostate, and colon cancers. Current research indicates vitamin D deficiency plays a role in causing seventeen varieties of different cancers as well as heart disease, stroke, autoimmune diseases, birth defects, and periodontal disease. [3] Vitamin D3 is believed to play a role in controlling the immune system (possibly reducing one's risk of cancers and autoimmune diseases), increasing neuromuscular function and improving mood, protecting the brain against toxic chemicals, and potentially reducing pain.[4]

Serum 25-hydroxyvitamin D [25 (OH) D] concentration is the parameter of choice for the

assessment of vitamin D status. Recently, many studies have used 30 ng/mL as a cut-off value and most experts now recommend the normal level of 25-hydroxyvitamin D (25OHD) to be 30 ng/mL. Vitamin D insufficiency is defined when the levels are between 20–29 ng/mL and at levels of d"20 ng/mL the patient is considered vitamin D deficient. [5]

Vitamin D deficiency is particularly common in individuals, those with chronic diseases, and Asians. Over the past decade, the relationship of vitamin D deficiency to the risk of developing diabetes mellitus (DM) and the risk for diabetic complications has been of great interest to scientists.

Wolf and colleagues examined incident hemodialysis patients, and found that diabetics were more likely to be severely 25(OH)-vitamin D-deficient (< 10ng/mL) than non-diabetics (22% vs 17%). [6] Lower 25(OH)-vitamin D levels and lower calcitriol levels strongly correlated with an increased risk for death during the first 90 days in patients not given injectable calcitriol or an analog.

Vitamin D is important for normal glucose metabolism. It acts through several mechanisms on glucose metabolism:

- Vitamin D directly acts on insulin producing cells (β cells) in the pancreas to produce more insulin.
- Vitamin D directly acts on the muscle and fat cells to improve insulin action by reducing insulin resistance.
- Vitamin D reduces inflammation which is commonly present in patients with Insulin resistance Syndrome and Type 2 diabetes.
- Vitamin D indirectly improves insulin production and its action by improving the level of calcium inside the cells.
- Studies have showed that Vitamin D supplementation can improve glycemic control in patients with Diabetes (Holick M)
- Further it can prevent/delay complications like neuropathy, nephropathy, retinopathy, diabetic ulcers (Joergensen C et al.,) [7]

Several observational studies have suggested that either low vitamin D levels or low vitamin D intake may predispose to the development of both type 1 and type 2 DM. The Nurses' Health Study found that vitamin D intake above 800 IU/day and more than 1200 mg of calcium per day were associated with a 33% reduction in the risk of developing type 2 DM compared with an intake of < 600 mg of calcium and < 400 IU of vitamin D. [8] A meta-analysis of largely observational studies concluded that there was a relatively consistent association between low vitamin D status, calcium or dairy intake, and prevalent type 2 DM or metabolic syndrome.[9]

AIMS AND OBJECTIVES : This study was conducted to assess the vitamin D status in prediabetics and newly diagnosed type 2 diabetic patients and correlate with other physical parameters like blood pressure, height, weight and body mass index (BMI).

MATERIALS AND METHODS : The study was carried out in the Department of Biochemistry from June 2017 to April 2018 after obtaining the approval of the Ethics Committee of Hi-tech Medical College, Rourkela. The prediabetic and newly diagnosed diabetic patients visiting the Medicine OPDs were selected and evaluated for Fasting Blood Glucose, Vitamin D levels and HbA1c. They were divided into three groups with the following criteria:

Group I: comprised of 40 age and sex matched healthy individuals

Group II: comprised of 30 patients with fasting plasma glucose level between 101-125 mg/dl and HbA1c levels >5.7-6.5%

Group III: comprised of 30 patients with FPG levels >125 mg/dl and HbA1c levels > 6.5%.

The following inclusion and exclusion criteria were used to form the patient groups:

Inclusion Criteria

- No prior history of Type 2 diabetes mellitus
- Written consent

Exclusion Criteria

- Renal failure
- Age < 18 years
- Malabsorption

Height, weight, and waist circumference were measured, and BMI was calculated for all the subjects. Pulse and BP were measured by manual sphygmomanometer in sitting position.

Fasting plasma glucose was estimated immediately after in automated analyzer (Erba Manheim EM 200) and HbA1c in D10 hemato analyzer. Vitamin D levels were estimated by chemiluminescence method by Seimens Hormone Analyzer.

Statistical analysis was performed using Graph Pad Prism and Microsoft Excel Sheet. Pearson correlation co-efficients were calculated online in SPSS software. For two-tailed p-values of <0.05 were considered significant, with 95% CIs.

RESULTS :

The age and sex distribution along with physical parameters as well as other calculated parameters are depicted in Table-1. The number of males in each group was more than the number of females. The average age in the groups were between 44-50 years, the highest being in group 2.

Table- 2, 3, 4 shows the comparison of means between different parameters between Control and Group 1, Control and Group 2, Group 1 and Group 2 respectively. BMI was significantly higher in group 1 and group 2 when compared with control group. However BMI did not show any significant increase in group 2 when compared with group 1. BP, FPG and HbA1c showed significant increase in both group 1 and group 2. The most important finding however was the fact that vitamin D levels significantly decreased in group 1 and group 2 compared to control. Moreover a significant fall in vitamin D level was found in group 2 compared with group 1.

BMI, FPG, HbA1c and significant correlation in both group 1 and group 2. However no significant correlations were found for both systolic and diastolic BP.

Table 1: Physical and other observed parameters with age and sex distribution in different groups

Parameters	Control (n=40)	Group 1 (n=30)	Group 2 (n=30)
Males	24	16	18
Females	16	14	12
Age (years)		46.4±4.03	47.33±8.88
BMI (kg/m^2)	22.67±1.77	24.11±1.86	25.38±2.96
Systolic BP (mmHg)	117.05±4.71	128.07±10.98	132.13±9.83
Diastolic BP (mmHg)	78.05±3.52	80.73±5.33	83.93±5.64
FPG (mg/dl)	86.06±8.05	109.83±8.23	153.2±26.93
HbA1c (%)	4.50±0.34	6.01±0.17	7.93±1.11
Vitamin D (ng/ml)	35.99±7.61	29.44±4.15	25.62±6.98

Table 2: Comparison of means between Control and Group 1

Parameters	Control	Group 1	p-value	Remarks
BMI (kg/m2)	22.67±1.77	24.11±1.86	0.0016	Significant
Systolic BP (mmHg)	117.05±4.71	128.07±10.98	<0.0001	Highly significant
Diastolic BP (mmHg)	78.05±3.52	80.73±5.33	0.0137	Significant
FPG (mg/dl)	86.06±8.05	109.83±8.23	<0.0001	Highly significant
HbA1c (%)	4.50±0.34	6.01±0.17	<0.0001	Highly significant
Vitamin D (ng/ml)	35.99±7.61	29.44±4.15	<0.0001	Highly significant

Table 3: Comparison of means between Control and Group 2

Parameters	Control	Group 2	p-value	Remarks
BMI (kg/m2)	22.67±1.77	25.38±2.96	<0.0001	Highly significant
Systolic BP (mmHg)	117.05±4.71	132.13±9.83	<0.0001	Highly significant
Diastolic BP (mmHg)	78.05±3.52	83.93±5.64	<0.0001	Highly significant
FPG (mg/dl)	86.06±8.05	153.2±26.93	<0.0001	Highly significant
HbA1c (%)	35.99±7.61	7.93±1.11	<0.0001	Highly significant
Vitamin D (ng/ml)	35.99±7.61	25.62±6.98	<0.0001	Highly significant

DISCUSSIONS:

Vitamin D has recently been associated with several of the contributing factors known to be linked to the development of type 2 DM, including defects in pancreatic βcell function, insulin sensitivity, and systemic inflammation. Several physiologic mechanisms have been proposed, including the effect of vitamin D on insulin secretion, the direct effect of calcium and vitamin D on insulin action, and the role of this hormone in cytokine regulation. [10,11] Although most studies indicating this relationship are observational, one meta-analysis showed a relatively consistent association between low vitamin D status, calcium or dairy intake, and prevalence of type 2 DM or metabolic syndrome. The study concluded that the highest type 2 DM prevalence, 0.36 (95% CI, 0.16–0.80), among participants who were not black was associated with the lowest blood levels of 25-hydroxyvitamin D. In addition, metabolic syndrome prevalence of 0.71 (95% CI, 0.57–0.89) was highest among those with the lowest dairy intake. There was also an inverse relationship between type 2 DM and metabolic syndrome incidences and vitamin D and calcium intake. [13].

This study showed that vitamin D levels are lower both in prediabetics and newly diagnosed diabetics when compared to normal population. Moreover FPG and Hba1c showed significant correlation with vitamin

D levels. There is also a possible link between BMI and vitamin D and obesity may increase the risk of vitamin D deficiency especially in diabetics.

CONCLUSION:

This study indicates there is a definite correlation between vitamin D levels and diabetes and prediabetes. Further risk of CVD, nephropathy, neuropathy and other complications are common in diabetes compared to normal population. Hence prudent use of vitamin D supplementation can help in mitigating/ delaying such complications. However our study was conducted on a small group, hence be taken only as a suggestion and prospective studies with larger patient group can conclude whether vitamin D supplementation can actually be helpful in progression of diabetes and preventing complications in diabetic patients.

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Case Report

INTERNAL CAROTID ARTERY THROMBUS AND CEREBRAL INFARCT FROM A LARGE LEFT ATRIAL MYXOMA : A RARE CASE REPORT

S. Sahoo[1], M.R Kundu[2], P.Jena[3], S. Behera[3], R. Mohanty[4]

ABSTRACT :

Atrial myxomas are benign tumors most often located in left atrium. Left atrial myxoma can present with wide variety of symptoms including cardioembolic stroke, accounting for lesser than 1% of all ischemic strokes. Now we report a rare case of left atrial myxoma leading to right internal carotid thrombus, MCA territory infarct and left hemiplegia.

INTRODUCTION :

Atrial myxomas represent approximately 50% of all cardiac tumors. About 75% of them are located in the left atrium, 18% from the right atrium. The few remaining tumors originate from atypical sites such as left or right ventricle and valves [1]. 30-40% of patients with myxoma present with systemic embolism (central and peripheral), out of them 50% suffer from cardioembolic stroke.

Atrial myxoma are rare cause of stroke accounting lesser than 1% of all ischemic strokes [2, 3].Here we report a case of young female (32 years) patient having large left atrial myxoma leading to right internal carotid thrombus, right MCA territory infarct and left hemiplegia.

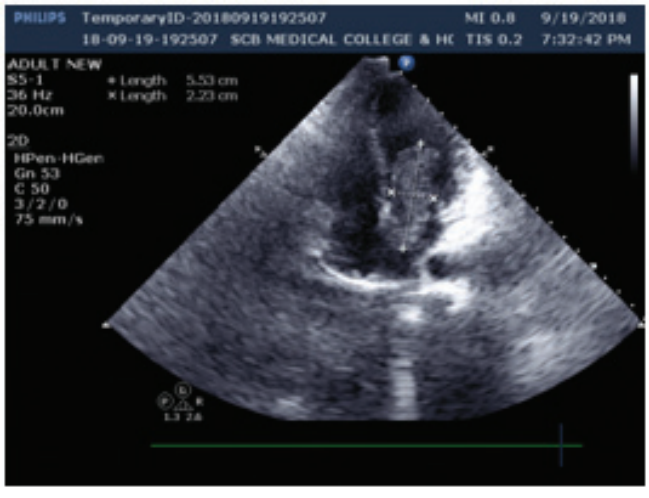
CASE REPORT :

A 32 year old woman was admitted with a 5 days history of sudden onset of vomiting, slurring of speech, and weakness of left upper and lower limb. There is no history of headache, fever, seizure or head trauma. She had off and on low grade fever with myalgia for last 4 years. None of her paternal family member had similar symptoms.

On examination the patient is conscious and oriented. She had pallor and pulse rate of 84/min, regular, normal in character, good volume, no brachio-femoral delay. Her Right carotid pulse was feeble with normally palpable peripheral pulses. Blood pressure was 110/70 mm of Hg. No significant difference of blood pressure was found in upper and lower limb. On neurologic examination, the patient was conscious, cooperative with spastic dysarthria. Left 7th cranial nerve palsy (UMN type) with left side spastic hemiplegia of power 2/5 around joints of upper and lower limb with extensor plantar response. On CVS examination, heart rate 80/ min, regular, first heart sound was loud. Other systemic examination revealed no abnormality.

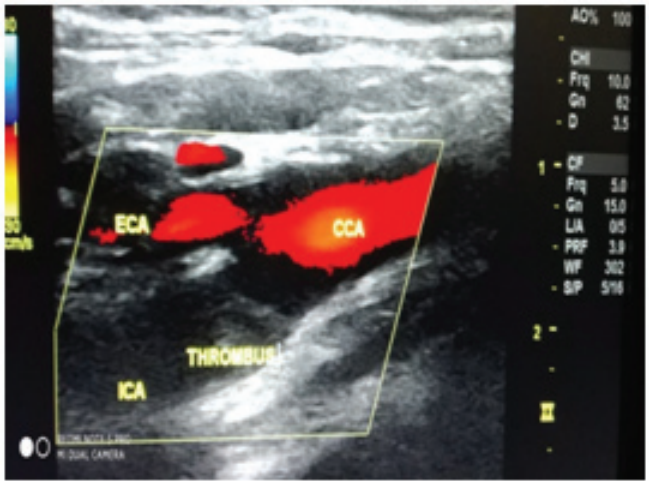
She had haemoglobin 8gm%, ESR 92mm/1st hour, CRP 9mg/L, RFT, LFT, PT, APTT and INR all within normal limits. Viral markers were negative. E.C.G., chest X-ray revealed no abnormality.

Her trans-thoracic 2-D echo showed heterogeneous mass of size 34mm*20mm attached to inter-atrial septum that protrude into left ventricle during diastole, suggestive of left atrial myxoma (fig.1). Ultrasound Doppler study detected right proximal internal carotid artery complete thrombus (fig.2). NCCT brain revealed right ganglio-capsular and fronto-parieto-temporal infarct in right MCA territory (fig.3).

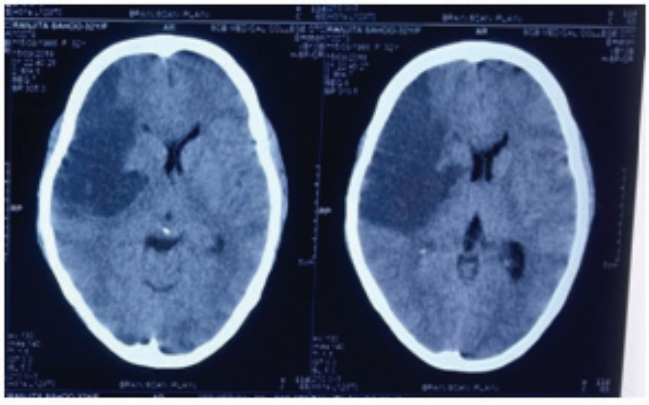


(Fig.1)

[4]Asso. Professor, [3]Asst. Professor
[2]Senior Resident, [1]PG Student
Dept. of Medicine, SCBMCH Cuttack



(Fig.2)



(Fig.3)

After inter-departmental (CTVS, Cardiology and Neurology) discussion, the patient was scheduled for resection of left atrial myxoma and thrombectomy after 4 weeks and discharged with antiplatelets.

DISCUSSION:

Cardiac myxomas remain the most common cardiac benign neoplasms, representing as many as 50% of all primary tumors of the heart[1],seen in third to sixth decades of life and show a 2:1 female preponderance[2]. It generally occurs as sporadic, but 7% of cases are familial. Carney syndrome is an autosomal dominant complex of cutaneous and cardiac myxoma, pigmentation and endocrine abnormalities[4,5]. The clinical features (Goodwin triad) include embolism, intracardiac obstruction and constitutional symptoms. 10-20% cases are asymptomatic[6].

Cardioembolic stroke due to atrial myxoma is less than 1% of all ischemic strokes[6]. The overlying thrombus on the surface of the myxoma plays a role in the embolic phenomena, rather than deciduous fragment of myxomatous tissue[4].Besides cardioembolic stroke, cerebral aneurysm and myxomatous metastasis were the other CNS complications. Embolism may occlude peripheral arteries as well as visceral, renal and coronary artery. Rarely complete occlusion of abdominal aorta by tumor emboli has been reported[7,8]. Here this patient has right internal carotid complete thrombus with right cerebral infarct (MCA territory) .

Left atrial myxoma usually causes mitral valve obstruction and can manifest as sudden onset dizziness, palpitations, dyspnoea, syncope and congestive heart failure and this is positional in nature, owing to the effects of gravity on position of tumour. Sometimes first heart sound is loud and a characteristic low-pitched sound “tumour plop” may be heard on auscultation. Mitral regurgitation also documented and resulted from tumour induced valvular trauma[7,9].

Constitutional signs and symptoms like fever, weight loss, cachexia, malaise, arthralgias, rash, and Raynaud’s phenomenon are present in about 50% of these patients and they may also have increased globulins, anaemia, raised ESR, CRP, thrombocytopenia or thrombocytosis. Therefore it may be misdiagnosed as having vasculitis, endocarditis, collagen vascular disease, or paraneoplastic syndromes [7].In this case the patient has pallor,raised ESR, CRP and history of constitutional symptoms.

Transthoracic echocardiography has a sensitivity of around 90%, where as transesophageal echocardiography has a sensitivity of 100% in detecting atrial myxoma[9].

Surgical excision of atrial myxoma gives excellent short term and long term results.There is no clear guideline for immediate medical management (systemic anticoagulation) for ischemic stroke and time interval from onset of stroke to time of the surgery[4,8]. The large dose of anticoagulation required for cardiopulmonary bypass may trigger hemorrhagic transformation. A study showed the mortality rate among the patients who undergone open heart surgery with a recent embolic stroke became considerably reduced if

the surgery was postponed more than 4 weeks after the neurologic events [10].

In this case as the patient approached after 5 days of onset of symptoms, the thrombolysis of carotid thrombus was not advised. Anticoagulation was unsuitable due to large infarct area with high risk of haemorrhagic transformation. So, this patient was scheduled for excision of myxoma and thrombectomy after 4 weeks.

CONCLUSION:

Atrial myxoma is the most common tumor of the heart. It can present as systemic embolisation, intracardiac obstructive symptoms and constitutional symptoms. It may cause thrombotic occlusion of abdominal aorta, carotid artery, coronary artery and peripheral vessels. It is an important differential diagnosis of young stroke.Due to constitutional symptoms, it may mimic vasculitis, endocarditis and collagen vascular disease. Left atrial myxoma is generally curable if surgically excised and prognosis is excellent.

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Case Report

SARCOIDOSIS PRESENTING AS RECURRENT LOWER MOTOR NEURON FACIAL PALSY- A CASE REPORT

L. Patnaik[1], S. Behera[2]

ABSTRACT

Sarcoidosis is a chronic inflammatory non-caseating granulomatous disease of unknown aetiology that affects many organs and tissues, most commonly the lungs. Neurosarcoidosis occurs in 5-10% cases[1] with cranial neuropathies being the most common manifestation of neurosarcoidosis. We report a case of neurosarcoidosis in a 17-year-old female presenting with recurrent with lower motor neuron facial nerve palsy.

Abbreviation:

ACE : Angiotensin Converting Enzyme, ESR: Erythrocyte Sedimentation Rate, CRP : C- Reactive Protein

INTRODUCTION

Sarcoidosis is a multisystem inflammatory disease of unknown aetiology that manifests as non-caseating granulomas. The lungs are affected most frequently but the eyes, skin, nervous system, heart, kidneys, bones and joints also may be affected. It often occurs in young adults and women are more susceptible than men (approx. 2:1). Neurosarcoidosis occurs usually in cases of sarcoidosis with substantial systemic involvement while strictly neurologic forms are seen in less than 10% of patients. Any cranial nerve may be affected and the most frequently affected cranial nerve is VII.

CASE REPORT

A 17-year-old female presented to medicine OPD, S.C.B Medical College, Cuttack with complaint of sudden onset of inability to close the left eye and drooling of saliva from left angle of mouth.

Her past history revealed she had suffered from similar symptoms on right side of face 3 months back and was diagnosed as right sided Bell's palsy. There was no history of fever, cough, breathlessness, arthralgia, skin rash, altered sensorium.

General examination revealed mild pallor, no icterus, clubbing, cyanosis, lymphadenopathy and oedema. Pulse- 72/min, regular; BP- 110/70 mmHg; respiratory rate- 16 per min; temperature- 98°F. Examination of cranial nerves showed bilateral lower motor neuron facial nerve palsy with left more than right. Other cranial nerves were found to be intact. There was no other motor or sensory deficit, plantar reflex was bilateral flexor and no cerebellar sign. Respiratory, cardiovascular system and abdominal examination revealed no abnormality. Ophthalmological examination was normal.

Laboratory investigations were: Hb-10gm%, TLC- 7000 Cu/mm, DC: N-85%, L-13%, E-2%; ESR-12mm, CRP-1.69 mg/L, Fasting Blood Sugar -75 mg/dl, 2hr Post Prandial Blood Sugar – 105 mg/dl; urea-14 mg/dl, creatinine- 0.8 mg/dl; Serum bilirubin (T) – 0.7 mg/dl, Serum bilirubin (D) – 0.2 mg/dl, AST – 21 IU/L, ALT – 27 IU/L, ALP – 160 IU/L, urine- normal; FT4 – 1.69 ng/dl;TSH ˇ ² <ˇ²ˇ 0.19 ìU/ml; Serum calcium - 10.8 mg/dl; NCCT Brain was normal ;Serum ACE : 115U/L (N:8.00-65.00), Chest X-Ray was normal and USG – Abdomen & Pelvis was normal.

With the above findings, the patient was diagnosed with sarcoidosis clinically and with laboratory finding of high serum ACE value. She was given a course of oral corticosteroids and improved.

DISCUSSION

Sarcoidosis is a systemic, multiorgan non-caseating granulomatous disorder which mostly affects the lungs, lymph node, eyes and skin[2]. Neurological complications though rare, are well-recognised. Most

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common neurologic syndrome is aseptic meningitis and cranial nerve involvement., most commonly facial nerve which may be bilateral. Other cranial nerves which may be involved are II, III, IV, VI and VIII. Other neurological manifestations documented in sarcoidosis are peripheral neuropathy, mononeuropathy, myopathy and psychiatric disorders.

Respiratory complaints are the common presentation of sarcoidosis in the form of cough and dyspnoea due to hilar adenopathy and pulmonary arterial hypertension. Other manifestations include cutaneous form presenting as erythema nodosum, lupus pernio and maculopapular rash; ocular as uveitis and dry eyes; hepatosplenomegaly, hypercalcemia and cardiomyopathy.

The diagnosis of sarcoidosis requires compatible clinical features, laboratory and pathologic findings. Laboratory value of serum ACE >2 times upper limit normal and pathological biopsy of affected organ, if possible, showing non-caseating granulomas help in making a diagnosis of sarcoidosis.

Here, we report an usual case of a young girl presenting with only recurrent bilateral lower motor neuron facial palsy in the absence of other systemic involvement with high serum ACE level suggesting a diagnosis of sarcoidosis.

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Case Report

EIGHT AND HALF SYNDROME WITH HEMIPARESIS – A POSSIBLE NINE SYNDROME : A CASE REPORT

D. Ramachandran[1], S. Mohapatra[1], N. Debata[1], S. Behera[2]

ABSTRACT

"Eight-and-a-half" syndrome is a condition involving the ipsilateral abducens nucleus or paramedian pontine reticular formation (PPRF), the ipsilateral medial longitudinal fasciculus (MLF), and the adjacent facial colliculus. We report the case of a 55-year-old man presenting with restriction of adduction and abduction of right eye and the restriction of adduction of the left eye associated right facial palsy and left hemiparesis popularly known as the "nine" syndrome adding a new dimension to "eight-and-a-half" syndrome.

INTRODUCTION

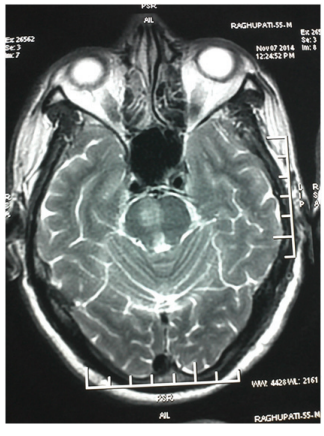
Pontine tegmental lesions usually present with gaze palsies, internuclear ophthalmoplegia (INO), nystagmus, and abducens palsy.(1) A combination of horizontal gaze palsy in one eye and INO in the other eye caused by a lesion in medial longitudinal fasciculus (MLF) or paramedian pontine reticular formation (PPRF) was first described in 1943 and subsequently, C Miller Fisher in 1967 coined the term one-and-a-half syndrome. (2) The combination of one-and-a-half syndrome with ipsilateral cranial nerve seventh palsy is known as eight-and-a-half. (3) Here, we present a patient who presented with clinical features of eight-and-a-half syndrome along with hemiparesis. This combination has often been called as the "nine" syndrome and is usually caused by any lesion in the dorsal tegmentum of the pons.

CASE REPORT

A 55-year-old man was presented with sudden onset of weakness of left half of the bodywith difficulty in speaking, giddiness and vomiting for 2 days. This was associated with doubling of vision.There was no history of loss of consciousness, fever, convulsions, dysphagia.There is no history of similar illness in the past. He was a known case of Type 2 DM, on irregular medication.

On examination, he was conscious, normally oriented with a PR-98/min and BP-142/90.Higher motor function was intact. Pupils were equal and reactive to light. Oculomotor abnormalities were noted in the form of right horizontal gaze palsy with limitation of abduction and adduction of right eye and limitation of adduction and abducting nystagmus of left eye (suggestive of right one and half syndrome). Adduction on convergence was preserved. Vertical eye movements were preserved Right lower motor neuron facial palsy was observed. Rest of the cranial nerves were normal. Motor examination revealed weakness of left upper limb and lower limb of grade 3/5 each. Sensory examination there was loss of proprioception on the left side.

Routine blood tests revealed no abnormalities. FBS was 140, PPBS was 230 mg/dl. ECG was also within normal limits. With a brain stem lesion in view of the clinical features, an MRI was done. MRI of the brain showed hyperintense ill marginated lesions involving the brainstem (right ponto-midbrain) region suggesting acute infarction in the basilar artery territory.



Hyperintense ill marginated lesions involving the brainstem(right ponto-midbrain) region.i.e. Acute infarction involving brainstem (B.A branches territory).

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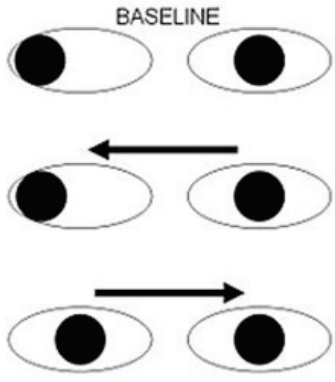
With this a diagnosis of right 8 and half syndrome with left sided hemiparesis, due to brain stem infarction involving the basilar artery territory, a possible "nine" syndrome was made. Patient was treated in the lines of an acute ischemic stroke and was subsequently discharged.

DISCUSSION

One-and-a-half syndrome represents ipsilateral conjugate horizontal gaze palsy (one) due to a lesion in the abducens nucleus or horizontal gaze center in the PPRF and an ipsilateral INO (half) due to a lesion in the MLF. (4)In brief, there is complete ipsilateral horizontal gaze palsy and partial contralateral horizontal gaze paresis (abduction preserved).



Additional involvement of intraaxial fasciculus of the facial nerve results in palsy of cranial nerve VII and this along with one-and-a-half syndrome constitute the eight-and-a-half syndrome.(3)

The anatomical localization is in the ipsilateral dorsal tegmentum of the caudal pons in one-and-a-half and eight-and-a-half syndrome. The prime etiologies for both syndromes are brain stem infarcts/hemorrhage, multiple sclerosis/brainstem demyelination,brain stem tumors, and arteriovenous malformations. (2) Several variants have been described. A case of eight-and-a-half syndrome, combined with ipsilateral vertical gaze palsy was reported by Marquart et al., (2013) due to involvement of midbrain reticular formation apart from dorsal pontine tegmentum(5).Rosini et al, in 2013 described a "nine" syndrome which comprised of eight-and-a-half syndrome with hemiparesis and hemihypoesthesia due to additional involvement of corticospinal tract and medial lemniscus by lacunar pontine infarction.(7) Variants with eight and half syndrome and hemiataxia have also been described. (2)

In the present case, the patient had clinical features suggestive of right eight-and-a-half syndrome due to infarction in right rostral pontine tegmentum with hemiparesis and hemihypoesthesia due to additional involvement of corticospinal tract and medial lemniscus by pontine infarction.

CONCLUSION

In conclusion the clinical features reported in this patient configure a relatively rare variant of eight and half syndrome, the "nine" syndrome. Recognizing such cases in clinical practice can lead help in their specific anatomical localization.

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Case Report

ANSA PANCREATICA-IN A YOUNG MALE PRESENTING AS ACUTE RECURRENT PANCREATITIS

N. Garabadu[1], D. Udayapuria[2]

Abstract

Acute Recurrent Pancreatitis(ARP) refers to a clinical entity characterized by episodes of acute pancreatitis which occurs on more than one occasion.Recurrence of pancreatitis occurs in normal morphofunctional gland.ARP can be identified in majority of cases, most common being alcohol, GSD, sludge, sphincter of oddi dysfunction and anatomical ductal variant interfering in pancreatic juice outlet.Before diagnosing as idiopathic variety,more aggressive investigation through MRCP and CT pancreaticography should be undertaken.

Keywords: Acute recurrent pancreatitis, etiopathogenesis-ansa pancreatica.

INTRODUCTION:

ARP is diagnosed retrospectively by clinical definition after only the 2nd episode of pacreatitis.It is characterized by self limited oedematous changes in pancreas.Acute episodes are generally mild to moderate requiring 1 to 3 days in hospital.Sometimes pancreatitis like pain with raised S.Amylase and Lipase lasts only a few hours and patient recovers without hospitalization.

The majority causes:-

Biliary pancreatitis-Gall stone disease & constriction of ampulla of vater-40%

Alcohol-30%

Idiopathic-20%

Others-10%(Metabolic/post ERCP/abdominal trauma/drugs/infections/

Radiotherapy/autoimmunity/penetrating ulcers).

We present a case of ARP in a young adult of age 23,where on further investigation by MRCP, a rare anatomical variant of pancreatic duct was found.

Case History:-

A male patient Mr.Pranay Bai,age 23 years was admitted to Health Care nursing home with complaints of recurrent abdominal pain associated with vomiting & pain was increased after food.He was hospitalized 3 times in past 1 year.Last attack of pain and vomiting occurred 3 days prior to hospitalization at Health Care.

No h/o alcohol/jaundice/medication/infection/ autoimmune disease/hyperpara- thyroidism/dyslipidemia/ trauma/or any history suggestive of gall stone disease.

On Clinical Examination:-

Afebrile,No pallor, icterus,or oedema.

Pulse-56/min, BP-100/70mm,Hg.

CVS/Chest/CNS no abnormality.

P/A-Soft,nontender, no hepato splenomegaly

BS +, no FF.

Investigations:-

S.Amylase-186 IU/L, ESR-28 mm/hr.

All other biochemical parameters normal.

UGIE-normal, Abd USG- normal

All previous hospitalization shows increased S.amylase and bulky pancreas.

So provisional diagnosis of "Acute Recurrent Idiopathic Pancreatitis" was made.

Further investigation with MRCP was done to find out possible cause.

MRCP revealed normal liver,hepatic duct,CBD and gall bladder.Pancreas showed altered signal intersity in head and body of pancreas.There was a branch of main pancreatic duct forming a loop and terminating into minor papilla(ANSA PANCREATICA).

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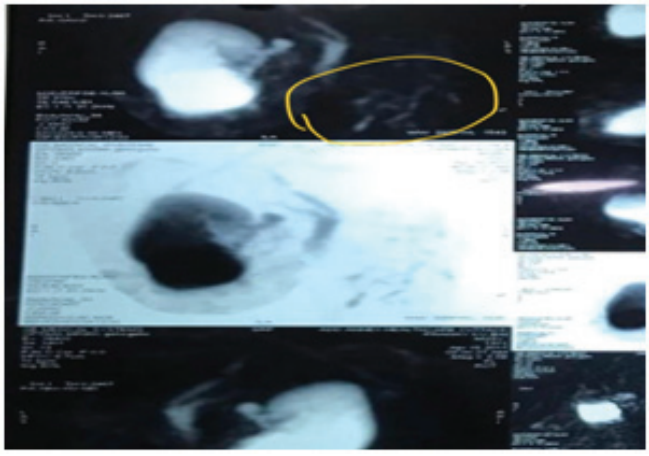
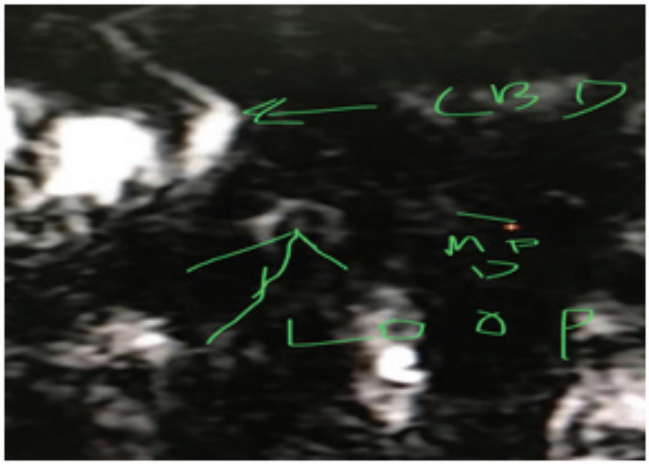


Figures:- (1)



Figures:- (2)

MRCP Picture 1 and 2 showing a branch of main pancreatic duct forming a loop and draining into minor papilla

DISCUSSION:-

"Ansa pancreatica" is a rare variety of anatomical variation of pancreatic duct.It arises as a branch duct from main pancreatic duct.It descends down initially and then ascends upwards,forming a loop and finally terminating at the minor papilla.

Recently "Ansa Pancreatica" has been considered as a pre disposing factor in patients with idiopathic ARP.The main variants commonly found are-

Meandering main pancreatic duct- 40%(inverted Z shaped abnormality).

Pancreatic divisum- 26%

Ansa pancreatica- 14%

Mechanical obstruction to pancreatic juice out flow in these variants is the cause of Recurrent Pancreatitis.

Finally, a diagnosis of 'Ansa Pancreatica' causing ARP was made in our young male patient.

CONCLUSION:-

Therefore it is suggested that in all ARP patients before labeling them as idiopathic variety MRCP and CT pancreaticography should be taken up to rule out microlithiasis and anatomical variations.

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Case Report

OROPHARYNGEAL DYSPHAGIA IN DERMATOMYOSITIS – A RARE CASE REPORT

H. Bhuyan1, M.R. Kundu2, P. Jena3, S.Behera3, R. Mohanty4

ABSTRACT:

Dermatomyositis is an inflammatory myopathy presenting with symmetrical proximal muscle weakness with characteristic rash. Dysphagia is not so common in dermatomyositis, with 1 year survival of approximate 31% and is usually associated with internal malignancy. We report a case of dermatomyositis without any internal malignancy presenting withdysphagia along with proximal muscle weakness.

INTRODUCTION:

Inflammatory myositis are a group of autoimmune connective tissue disorders characterized by progressive and symmetric proximal muscle weakness, except in inclusion body myositis (IBM). Dermatomyositis (DM) is differentiated from polymyositis (PM) by presence of characteristics skin rash like heliotrope rash, gottron ˇ s papule, shawl sign. Clinical manifestations of DM are heterogenous and dysphagia and internal malignancy affects the prognosis.

Dysphagia has been reported in 10-73 % patients with inflammatory myopathy during clinical course, especially in IBM. Dysphagia primarily affects skeletal muscle-activated oropharyngeal phase of swallowing due to weakness of oropharyngeal, laryngeal, oesophageal musculature. Recognition of dysphagia is important as it is associated with impaired quality of life and poor prognosis. It has been reported that dysphagia involvement is more frequent in patients with internal malignancy ,anti-TIF-1¥ Ab, elderly males, without ILD,among patients with DM.

CASE REPORT:

Here we reporta rare case of young male presenting with symmetrical proximal muscle weakness and dysphagia, negatively screened for internal malignancies.

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A 31year male patient presented with chief complaints of weakness of all four limbs for 5 months followed by nasal regurgitation and inability to swallow. On examination patient was tachypnoeic with presence of heliotrope rash, gottron papule, shawl sign. CNS examination showed reduced muscle bulk, tone and reduced power around all joints with proximal muscle weakness (grade 2) being more than distal muscle weakness (grade 4).He was unable to hold his neck. DTR were absent and b/l plantar flexor. Respiratory system examination showed coarse crepitations over b/l infra-scapular and infra-axillary areas. A provisional diagnosis of dermatomyositis was made. It was differentiated from polymyositis by presence of typical rash and from inclusion body myositis as IBM involves elderly individuals with asymmetric pattern of involvement and absence of typical dermatomyositis rash. In fact IBM is adiagnosis of exclusion.

Investigations showedTLC-9200 (eutrophil-70% and lymphocytes-35%) raised inflammatory markers(ESR-70, CRP(Q)-12.5), CPK-3321, TSH-0.9, SGOT-273, SGPT-94, ALP-280,RFT normal, ENA profile negative, EMG showed myopathic pattern. On screening for internal malignancies MRI BRAIN normal, digital chest x-ray-normal, HRCT THORAX showed left lower lobe patchy areas of ground glass opacities and consolidation with apical segment of left lower lobe showing centrilobular nodular with tree in bud pattern, stool occult blood-negative, CECT ABDOMEN showed mild hepatomegaly with calcific foci in back and gluteal muscles. 2D ECHO-normal.

A pulse methylprednisolone(500mg) was given for 3 days and then discharged with tablet omnacortil (50mg) and was followed-up after 1month. There was improvement in muscle power and dysphagia on follow up.

DISCUSSION:

The idiopathic inflammatory myopathies are divided into four subgroups: 1.dermatomyositis (DM)

2. polymyositis (PM)3.inclusion body myositis (IBM) and 4.overlap syndrome with mixed characteristics .Diagnostic criteria for PM and DM established by BOHAN and PETER in 1975. Individual criteria are 1) symmetrical proximal muscle weakness 2) muscle biopsy evidence of myositis 3)increase in serum skeletal muscle enzymes 4) characteristic EMG pattern 5) typical rash of dermatomyositis. Definite if 4 criteria +, probable if 3 criteria +, possible if 2 criteria + .DM is differentiated from PM by its characteristic skin rash (heliotrope rash, shawl sign, gottron papule, holster sign).DM is associated with an occult malignancy in 30% of cases especially colorectal, bladder, lung, non-Hodgkin's lymphoma, ovarian, pancreatic and stomach cancers. The risk for developing a cancer remains for up to five years. A poorer prognosis is associated with old age, non-white race, occurrence with an underlying malignancy, bulbar involvement, cardio-respiratory involvement and delayed treatment.An incidence of 10 cases per 100,000 individuals has been reported, affecting women more commonly with a ratio of 2:1. Adults and children are equally affected, with the peak incidence between the ages of 45 and 64 in adults.

Clinical features include fatigue, proximal muscle weakness, muscle tenderness, Dysphonia, dysphagia, breathlessness. Extra-muscular manifestations include fever, Raynaud's phenomenon, subcutaneous calcifications and arthralgia. The characteristic rash can occur over the shoulders, upper arm and back resulting in the termed "shawl sign", symmetrically over upper eyelids as a violaceous to dusky erythematous rash with or without oedematermed "heliotrope rash", over knuckles, MCP, PIP, DIP as "gottron papule", on lateral thigh termed "holster sign" , as V-sign

Investigations should include full blood count, urea and electrolytes, liver function tests (transaminases may be raised), creatine kinase (CK). A chest radiograph,an ECG, echocardiogram should be performed if cardio-respiratory involvement is suspected. Anti-nuclear antibodies (ANA) are positive in 80% of patients, while anti Jo-1 antibodies are positive in approximately 20%,predictive of pulmonary involvement. Anti-Mi2 occurs in 25-30% patients, almost specific for DM. patients with antiSRP antibody has a worse prognosis than anti-Mi2 antibodyCK levels are used to monitor disease activity but levels may have poor correlation with clinical disability. Patients are screened for an occult malignancy with investigations that include computed tomography of the abdomen, chest and pelvis, mammography and serum tumour markers. MRI has been used to successfully to identify myositis of affected muscle groups, as muscle oedema correlates well with inflammatory changes. A muscle biopsy is still required to make the diagnosis. Classical findings include endomysial inflammation predominant in the perivascular regions or in the interfascicular septae, and around the fascicles.

CONCLUSION:

There are literatures demonstrating increased frequency of dysphagia in DM patients with internal malignancy and in elderly males. Previous reports showed development of dysphagia during long course of disease, but this is a rare case report of a young male of dermatomyositis without any detected internal malignancy presenting with dysphagia within a short course of disease.

Principal treatment for DM is corticosteroids (1mg/kg). Steroid resistant disease is not uncommon, and methotrexate, azathioprine, cyclosporine and cyclophosphamide have all been used successfully. Intravenous Immunoglobulin (IV IG) has been used in patients refractory to steroid sparing treatment. The dose recommended in the literature is 2 g/kg, to be repeated in six weeks depending upon clinical response. IV IG is treatment of choice in dysphagia with dermatomyositis.

All patients of DM presenting with dysphagia must be screened for internal malignancies and must be treated immediately as it is associated with poor prognosis.

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Review Article

GESTATIONAL DIABETES MELLITUS

D. Patro[1], S.S. Mangaraj[2], A.K. Choudhury[3], A.K. Baliarsinha[4]

Introduction :

Gestational diabetes mellitus (GDM) is one of the most common medical complications of pregnancy. The disease has important health implications for mother and child. GDM is defined as glucose intolerance with onset or first recognition during pregnancy(1), regardless of whether the condition may have predated the pregnancy or persisted after the pregnancy. GDM is diabetes that is first diagnosed in the second or third trimester of pregnancy that is not clearly either preexisting type 1 or type 2 diabetes.

Epidemiology :

The prevalence of GDM in India varied from 3.8 to 21% in different parts of the country, depending on the geographical locations and diagnostic methods used. GDM has been found to be more prevalent in urban areas than in rural areas (2). The overall incidence rate of GDM was higher in Asian (17%) and Hispanic (11%) women and lower rates in non-Hispanic white (7%) and black (7%) women(3).

Pathogenesis of GDM :

GDM is a disease of the pancreatic â cells, which do not produce sufficient insulin to meet the increased requirements of late pregnancy. The â-cell defects that underlie GDM occur is that of obesity and chronic insulin resistance. The role of the acquired insulin resistance of pregnancy in the pathogenesis of the hyperglycaemia that defines GDM has evolved over time. It has been thought that GDM develops when â cells fail to keep pace with the increasing insulin resistance that occurs during the second half of pregnancy(4). The resultant increasing imbalance between insulin demand and supply manifests itself as rising glucose levels, especially during the second half of pregnancy when insulin resistance is the greatest.

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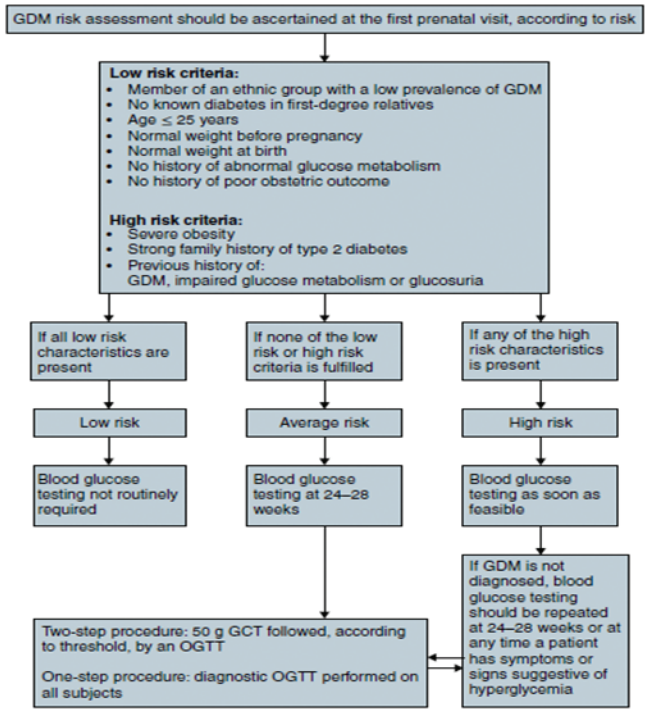
Importance of GDM :

Results from the HAPO (5) study provide useful insight into the frequency of perinatal complications in women with relatively mild GDM in the absence of treatment. In the HAPO study, women found to have fasting plasma glucose levels of >5.8 mmol/l or a glucose level of >11.1 mmol/l on the 75 g, 2 h OGTT were referred for treatment of GDM. Women with lower glucose levels than these thresholds received no diagnosis or care related to their glycaemic control. Risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks of gestation. Pre-eclampsia, preterm delivery, primary caesarean delivery, shoulder dystocia, neonatal hypoglycemia, neonatal hyperbilirubinemia, birthweight > 90th percentile, cord C-peptide > 90th percentile, percent body adipose tissue content > 90th centile was more in GDM than in non GDM.

Screening and Diagnosis :

Screening recommendations range from the inclusion of all pregnant women (universal) to the exclusion of all women except those at risk (selective). Screening policy should be determined locally, depending upon population characteristics,local prevalence and preference. There is debate regarding the preferred screening protocol for GDM. Some experts recommend universal screening because not all women who develop GDM have risk factors. The ADA policy states that screening done depending upon risk factors. The American Congress of Obstetricians and Gynecologists (ACOG) (6) recommends universal screening for all pregnant women, to be done between 24–28 weeks of gestation, except women who meet all the low-risk criteria. The United States Preventive Services Task Force on Preventive Health Care concluded that there is not enough evidence to support or deny universal screening for GDM (7)



Strategy for screening and diagnosis of gestational diabetes mellitus

(Source - Yoel Toledano, et.al. Diabetes in Pregnancy ; International Text Book Of Diabetes Mellitus, 4th Edition, Volume 2, Wiley Blackwell, 2015, 825)

Diagnostic Criterias :

GDM diagnosis can be accomplished with either of two strategies:

1. "One-step" 75-g OGTT or

2. "Two-step" approach with a 50-g (nonfasting) screen followed by a 100-g OGTT for those who screen positive.

One-step method (IADPSG defined diagnostic cut points)

Performa 75-g OGTT,with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28weeks of gestation in women not previously diagnosed with overt diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

1) Fasting: 92 mg/dL (5.1 mmol/L)

2) 1 h: 180 mg/dL (10.0 mmol/L)

3) 2 h: 153 mg/dL (8.5 mmol/L)

Two-step method

Step 1: Performa 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

If the plasma glucose level measured 1 h after the load is 130mg/dL, 135mg/dL, or 140mg/dL, proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made if at least two of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h during OGTT) are met or exceeded:

Carpenter-Coustan	or	NDDG
1) Fasting	95 mg/dL	105 mg/dL
2) 1 h	180 mg/dL	190 mg/dL
3) 2 h	155 mg/dL	165 mg/dL
4) 3 h	140 mg/dL	145 mg/dL

IADPSG - International Association of the Diabetes and Pregnancy Study Groups.

NDDG - National Diabetes Data Group

One step method - This one-step strategy was anticipated to significantly increase the incidence of GDM (from 5–6% to 15–20%), primarily because only one abnormal value, not two, became sufficient to make the diagnosis. (8). The increase in the incidence of GDM could have a substantial impact on costs and medical infrastructure needs. However ADA recommends these diagnostic criteria with the intent of optimizing gestational outcomes because these criteria were the only ones based on pregnancy outcomes rather than end points such as prediction of subsequent maternal diabetes.

Two step method – Screening with a 50-g GLT does not require fasting and is therefore easier to accomplish for many women. Treatment of higher-threshold maternal hyperglycemia, as identified by the two-step approach, reduces rates of neonatal macrosomia, large-for-gestational-age births (9), and shoulder dystocia, without increasing small-for-

gestational-age births. ACOG currently supports the two-step approach (10) but most recently noted that one elevated value, as opposed to two, may be used for the diagnosis of GDM.

Management :

After diagnosis, treatment starts with medical nutrition therapy, physical activity, and weight management depending on pregestational weight. Glucose monitoring aiming for the targets recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (11):Fasting, 95 mg/dL and either One-hour postprandial, 140 mg/dL or Two-hour postprandial, 120 mg/dL.

Medical Nutrition Therapy :

All women with GDM should receive nutritional counseling. The meal pattern should provide adequate calories and nutrients to meet the needs of pregnancy. The expected weight gain during pregnancy is 300 to 400 gm/week and total weight gain is 10 to 12 kg by term. Hence the meal plan aims to provide sufficient calories to sustain adequate nutrition for the mother and fetus and to avoid excess weight gain and post prandial hyperglycemia. Calorie requirement depends on age, activity, pre pregnancy weight and gestational weeks of pregnancy. Approximately 30 to 40 Kcal/kg i.e. an increment of 300 kcal/day above the basal requirement is needed in 2nd and 3rd trimesters. Those who meet glucose goals after a week of medical nutrition therapy can safely perform self-monitoring of blood glucose every other day, rather than daily (12).

Pharmacological Therapy :

Insulin is the first-line agent recommended for treatment of GDM in the U.S. While individual randomized controlled trials support the efficacy and short-term safety of metformin (13) and glyburide (14) for the treatment of GDM, both agents cross the placenta.

Insulin : Insulin may be required to treat hyperglycemia. Both multiple daily insulin injections and continuous subcutaneous insulin infusion are reasonable alternatives, and neither has been shown to be superior during pregnancy (15). Preferable to start with Premix insulin 30/70 at 0.5 – 1 U/kg/day and total insulin dose per day can be divided as 2/3 in the morning and 1/3 in the evening. Rapid acting insulin analogues, have been found to be safe and effective in achieving the targeted post prandial glucose value during pregnancy (16). The physiology of pregnancy necessitates frequent titration of insulin to match changing requirements. They should be advised to perform self monitoring of blood glucose (SMBG) on a daily basis, failing which, at least weekly monitoring should be encouraged. If self-monitoring is not possible, laboratory venous plasma glucose has to be estimated for adjusting the dose of insulin.

Glyburide : Glyburide was associated with a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin in a 2015 systematic review (17).

Metformin : Metformin was associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin in 2015 systematic reviews (18); however, metformin may slightly increase the risk of prematurity. Patients treated with oral agents should be informed that they cross the placenta, and although no adverse effects on the fetus have been demonstrated, long-term studies are lacking. Randomized, double-blind, controlled trials comparing metformin with other therapies for ovulation induction in women with polycystic ovary syndrome have not demonstrated benefit in preventing spontaneous abortion or GDM (19), and there is no evidence-based need to continue metformin in such patients once pregnancy has been confirmed (20).

Post Partum Follow up :

An OGTT with 75 g oral glucose, using WHO criteria for the non-pregnant population should be performed at 4-12 weeks post-partum. GDM is associated with an increased lifetime maternal risk for diabetes estimated at 50–70% after 15–25 years (21), women should also be tested every 1–3 years thereafter if the 4- to 12-week 75-g OGTT is normal, with frequency of testing depending on other risk factors including family history, prepregnancy BMI, and need for insulin or oral glucose-lowering medication during pregnancy.

Conclusion :

GDM is a problem that affects a significant number of women during pregnancy. GDM can have lasting health impacts on both the mother and the fetus.

In order to circumscribe and minimize potential complications to both mother and child, screening, diagnosis, and management of hyperglycemia are critical.

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Update Article

CARDIOVASCULAR OUTCOME TRIALS IN TYPE 2 DIABETES : A REVIEW OF WHAT HAVE WE LEARNED FROM THE PAST AND PRESENT

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Introduction :

The risk of cardiovascular disease (CVD) is twice in people with type 2 diabetes when compared to people without diabetes after adjustment for established cardiovascular (CV) risk factors [**1**]. Prospective epidemiological and experimental studies have reported an association between suboptimal glycaemic control [measured by an elevated glycated haemoglobin (HbA1c)] and both micro and macro vascular complications [**2**,**3**]. It was found that the relative risk for coronary heart disease (CHD) or stroke has been estimated at 1.18% (95% CI: 1.10-1.26) for every 1% increase in HbA1c [**4**]. In recognition of the graded relationship between glycaemic control and CV events a major shift has taken place in the recent years to develop evidence based treatment strategies for type 2 diabetes that will not only reduce the disease progression but will also reduce the CV disease burden and will prolong life.

Nissen and Wolski published a meta-analysis in 2007 suggesting that rosiglitazone was associated with significant risk of myocardial infarction (MI) and with increase risk of death from CV causes [**5**]. Their finding initiated an intense debate about the CV safety of the antidiabetic drugs and led to a remarkable change in the landscape of subsequent diabetic trials that have been conducted over the last few years. The US FDA revised their approval process for newer antidiabetic agents recommending that apart from lowering HbA1c which remains an acceptable primary efficacy endpoint sponsors should demonstrate that the therapy does not increase CV risk to an unacceptable extent [**6**]. The guidance also suggested that if the premarketing application contains clinical data that showed that the upper bound of the two-sided 95% confidence interval (CI) for the estimated increased risk (i.e., risk ratio) is between 1.3 and 1.8, and the overall risk benefit analysis supports approval, a post marketing trial will be needed to definitely show that upper bound of the two-sided 95% CI for the estimated risk ratio is less than 1.3. This essentially meant that the trials needed to be adequately powered and should include patients who are at higher risk of CV events, such as patients with relatively advanced disease, elderly and patients with some degree of renal impairment [**6**]. This has led to a plethora of CV outcome trials with glucose lowering agents in type 2 diabetes which are mostly and typically event-driven and are conducted to satisfy regulatory requirements in the shortest possible time. Majority of these trials are simple placebo controlled non-inferiority study designs which aims to show an absence of cardiovascular toxicity based on end point events. As per guidance, in majority of the studies major adverse CV events (MACE) has been selected as a primary end point which include CV mortality, MI and stroke and also includes hospitalization for acute coronary syndrome, urgent revascularization procedures and heart failure (HF) [**7**]**.**

Cardiovascular outcome trials from the past :

The pathophysiological process which drives CV disease in the diabetic population is complex and the clinical outcome is influenced by multiple pathways and needs interventions in different causal pathways simultaneously. Accelerated atherosclerosis is one such mechanism which influences increased risk of CV disease in type 2 diabetes. Surrogate endpoints like

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"optimal glycaemic control" monitored by HbA1c may actually fail to reflect the true clinical outcome hence most of the CV trials now focus on cardiovascular endpoints like CV death, fatal or non-fatal MI and stroke. In the past large scale landmark trials like United Kingdom Prospective Diabetes Study (UKPDS) have tried to address the effects of HbA1c lowering on CV outcomes [**8**,**9**]. In this trial, the effect of intensive glucose lowering on micro vascular effects were undisputed (25% relative risk reduction, p=0.0099) after a follow up of 10 years compared to the conventional therapy but the relative risk reduction for MI reached borderline significance only (16%, p=0.052) and there was no significant reduction in all cause death, stroke or composite of any diabetes related end point [**8**,**9**]. It was only with a further 10 years of post interventional trial follow up, significant risk reductions were noted for MI (15%, p=0.01) and all cause mortality (13%, p=0.007) in the former intensive group with greater results in the metformin subgroup [**10**].

Further large scale studies have tried to evaluate the efficacy of intensive versus standard glucose lowering strategies on CV outcomes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial with a median follow up of 3.7years showed a significant decrease rate of -fatal MI but was stopped prematurely because of an unexpected 22% increased relative risk of all cause mortality from CV deaths in the intensive treatment group [**11**]. The Action in Diabetes and Vascular disease: Preterax and Dimicron MR Controlled Evaluation (ADVANCE) trial had a median follow up of 5 years and reported a statistically significant 10% reduction in the primary endpoint of major macro vascular and micro vascular events in the intensive glycemic group (HR: 0.90, 95% CI: 0.82-0.98) but when analysed separately the effect on macro vascular outcomes were not significant (HR: 0.94, 95% CI: 0.84- 1.06) [**12**]. The Veterans Affairs Diabetes trial (VADT) included a similar standard treatment and an intensive therapy arm with a median follow up of 5.6 years. It didn't find any significant benefit in time to the first occurrence of a CV event in the intensive group (HR: 0.88; 95% CI, 0.74-1.05; p=0.14) and the observed event rate was 33.5% in the standard and 29.5% in the intensive group respectively with a relative reduction of11.9%. There was no significant difference between the twogroups in any component of the primary outcome or in the rate from death from any cause (HR: 1.07; 95% CI, 0.81-1.42; p=0.62). The conclusion from this trial was very similar to other trials like ADVANCE, ACCORD which didn't show any association between intensive glycemic control and risk reduction of CV events [**13**]. All these trials [**11-13**] had large sample size and up to 5 years of follow up, but they only showed non-significant trends towards reduced risk in their primary cardiovascular endpoints with allocation of intensive glycemic therapy. These trials enrolled patients with long standing diabetes and it remains a topic of debate whether the response would have been different in a newly diagnosed diabetes population but it reliably proved the principle that glycemic control alone is not a reliable surrogate marker for reduction of CV events. However, a meta-analysis by Turnbull et al of these three trials together with first 5 years of follow up data from UKPDS showed a significant reduction of MACE and particularly a risk reduction in MI with intensive glucose lowering [**14**]. There were other trials which looked into CV events and mortality endpoints and did not solely concentrate on glucose lowering strategies. In the RECORD trial [**15**] rosiglitazone was associated with higher risk of death or HF related hospitalization (HR: 2.10, 95% CI: 1.35-3.27) but in the post marketing study, no excess risk of CV events were noted other than HF and meta-analyses including RECORD have not shown convincing harm beyond the previously known excess risk of HF [**16**]. The PROactive study compared the use of pioglitazone with placebo added to usual diabetes care. In their follow up of more than 5000 patients for an average duration of 34.5 months they found a non significant trend for a 10% relative risk reduction in the primary composite CV end point but showed an increased incidence of HF. Although HF was not a pre-specified endpoint in this trial but the hazard ratio for hospital admission for HF was high in the pioglitazone group (HR: 1.41, 95% CI, 1.1-1.8, p=0.007) [**17**]. The earlier trials focussed on whether the changes in glycaemic control (monitored by HbA1c) would reduce CV risk and would produce beneficial effect but to postulate such an outcome patients needed longer follow up.

Recent cardiovascular outcome trials :

The US FDA and European Medicines Agency's (EMA) requirement for CV safety of hypoglycaemic agents in addition to glycaemic efficacy has lead to a paradigm shift by which recent CV outcomes trials are conducted. In order to comply with the regulatory requirements large scale studies have been and are being conducted which involves huge sample size, multiple countries with geographic and demographic variations and for a shorter follow up period and it is expected that majority will be reported by 2020 [**18**]. The major surprise that has sprung up is that majority of these trials are using a non-inferiority design which essentially shows that the new drug is not materially worse than the control. It seeks to show that any difference between the two treatments is small enough to allow a conclusion that the new drug has at least some effect or, in many cases, an effect that is not too much smaller than the active control[**19**]. The downside on a non-inferiority design is that it will aptly demonstrate the safety of the drug with minimal focus on its efficacy. Moreover the limited timeline allotted for these studies may potentially predict no harm in the high risk groups for CV disease but extended follow up periods are usually required to detect safety signals in low risk patients [**20**]. In the last few years there is a wave of cardiovascular intervention trials which have been conducted with the di-peptidyl peptidase 4 inhibitors (DPP-4). In the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial with a median follow up of 1.8 years, Alogliptin was studied as an addition to existing anti-hyperglycaemic treatment in comparison to a placebo in patients with type 2 diabetes who had an acute coronary event in the last 15-90 days prior to randomization. The study showed that a primary end point (composite death from CV disease, non-fatal MI, non-fatal stroke) was 11.3% in the Alogliptin group compared to 11.8% in the placebo group (HR: 0.96, upper boundary of one sided repeated CI, 1.16: $p< 0.001$ for non- inferiority) suggesting that the rates of major CV events were not raised with Alogliptin in comparison to a placebo [**21**]. This was followed by the results from the Saxagliptin Assessment of Vascular Outcomes recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial with a median follow up of 2.1 years which evaluated saxagliptin against a placebo showing similar results for a cardiovascular primary endpoint (7.3% and 7.2% respectively, HR: 1.00; 95% CI 0.89 to 1.12, $p=0.99$ for superiority and $p<0.001$ for non-inferiority). This suggested that saxagliptin did not increase or decrease rate of ischemic events but an unexpected outcome showed patient in the saxagliptin group with an increased admission with heart failure compared to the placebo (3.5% Vs 2.8%, HR: 1.27; 95% CI 1.07-1.51, $p<0.007$) [**22**]. The possible explanation for this was shown in a later sub-analysis which concluded that subjects who had greater risk of hospitalization with HF were those who had an eGFR <60 mls/min, had previous history of heart failure and with elevated baseline levels of N terminal pro B type natriuretic peptide (NT-proBNP) [**23**]. The latest published data reflecting a similar trend was in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) where patients had a median follow up of three years and showed that sitagliptin was considered to be non-inferior to placebo for primary composite CV outcomes (HR: 0.98; 95% CI, 0.88 to 1.09; $p<0.001$) and the total number of primary outcome that occurred were 11.4% in sitagliptin group in comparison to 11.6% in the placebo group. Moreover the rate of hospitalization for heart failure did not differ between the two groups (HR: 1.00; 95% CI, 0.83 to 1.20; $p=0.98$) [**24**]. The population that were studied in these three trials [**21-24**] were very similar and the patients had well managed cardiovascular and glycemic risk factors at baseline. These trials also suggested that the catalytic inhibition of DPP-4 is basically safe for the CV standpoint but such inhibition alone is insufficient to improve CV outcomes in such short term and longer follow up is necessary. Most of the CV outcome trials with the DPP-4 inhibitors were conducted in a placebo controlled setting with no active comparator. This leads to a limitation in clinical interpretation and did not allow an assessment of comparative effectiveness. Sulfonylurea's (SU) have been always recommended to be the preferred second line agents for type 2 diabetes after metformin and there have been uncertainty of its long term CV safety in the University group Diabetes Programme (UGDP) [**25**]. It is uncertain whether the UGDP findings are

applicable to modern clinical management of diabetes but a recent meta-analysis of 40 randomized controlled trials (RCT's) didn't show any increased risk of macro vascular disease and all cause mortality with second generation SU's versus other oral agents or placebo [**26**]. As the DPP-4 inhibitors are often considered to be the second line agents, the Cardiovascular outcome study of Linagliptin versus Glimiperide in patients with type 2 diabetes (CAROLINA) will stand out which compares Linagliptin with an active SU comparator, glimiperide for CV safety. As CAROLINA has no placebo group to calibrate any findings to the population being studied a second study called Cardiovascular safety and Clinical Outcome with linagliptin (CARMELINA) is being carried out by the same sponsors who will compare the CV and renal safety of linagliptin versus placebo when added to standard care in type 2 diabetes. This will be the first large scale outcome study dedicated for evaluating of tangible renal outcomes with a DPP-4 inhibitor in comparison with a placebo and the results will be expected after 2018 [**27**][**28**]. In the other subclasses of oral hypoglycaemic agents the Sodium Glucose Transporter 2 (SGLT 2) inhibitors have generated avid interest in the last few years. The multicentre trial to evaluate the effect of Dapagliflozin on the incidence of cardiovascular events (DECLARE-TIMI 58) [**29**] is currently ongoing and assessing the impact of SGLT 2 inhibitors on the CV risk for MACE. The CANVAS AND CANVAS –R with canagliflozin done in type 2 diabetic patients with cardiovascular diseases found that patients treated with this drug had a lower risk of cardiovascular events than those who received placebo but had a greater risk of amputation primarily at the level of toe or metatarsl.The EMPERAG with empagliflozin done in type 2 diabetics with pre-existing cardiovascular disease also found that those who received the drug had a lower rate of primary composite cardiovascular outcome and of death from any cause versus those who were taking placebo.Similarly the SUSTAIN -6 with GLP-1 agonist semaglutide done in type 2 diabetics with cardiovascular disease found the rate of cardiovascular death, non fatal myocardial infarction or non fatal stroke was significantly lower among the drug users versus placebo users . A major challenge for the clinicians currently is to make the right choice for the patients in determining which oral agents will be most effective for reducing blood glucose and would also minimise CV risk. To add the on going debate and to the wealth of data that is available with the newer agents and to close the gap on uncertainties concerning earlier agents, the Thiazolidinediones or Sulfonylurea's and Cardiovascular Accidents Intervention Trial (TOSCA.IT) has been designed by the Italian Society of Diabetology [**32**]. This is a randomized, parallel group, non-blinded trial which is purely an institutional trial and not supported by any industry. This trial has been drafted as a head to head comparison between pioglitazone and SU's. It will provide evidence based information between two old, widely used and less expensive drugs used for management of diabetes when metformin alone is not effective. Moreover, it will also throw light on the primary efficacy outcome and several secondary outcomes over a follow up period of 48 months.

Current challenges of cardiovascular outcome trials :

As cardiovascular disease remains the leading cause of mortality and morbidity in type 2 diabetes it is imperative that the benefit and risk of oral agents are defined appropriately. The current generation of CV outcome trials needs a significant revamp as majority of them are short lived, measuring limited outcomes at a very high cost. The non-inferiority design has ballooned following guidance from the regulatory authorities like US FDA, EMA and similar regulatory bodies across the world. The designs of recent trials also limits direct head to head comparative analysis and puts significant constraints in studying long term clinical outcomes which is related to a chronic disease like type 2 diabetes. It is understandable that long term trials will incur more cost and will have problems with retention and adherence. In the current climate, the studies are larger and more comprehensive and include CV high risk patients but the need to conduct such post approval CV outcome studies the sponsors are shelling out an enormous amount of money. Currently, the huge market for drugs relating to type 2 diabetes is enabling the pharmaceutical companies to bear the cost of such trials but every company may not have the same expertise and resources which will serve as a major hindrance to smaller units for developing anti-

diabetes medicines in the future. Several countries do not need CV outcome data for the approval of anti-diabetic medications which would suggest that future trials needs comprehensive designs which takes in to account the choice of patient population, demographic and cultural differences, local practices , heterogeneity of treatment effect and also focus on cost. These studies should also have extended follow up for better characterization of efficacy and safety profiles of drugs intended to treat chronic diseases like diabetes.

Conclusion :

CV disease will always remain an integral aspect of diabetes management. Although previous long term studies have shown the benefit of risk reduction in micro vascular complications with intensive glucose lowering but none have shown similar beneficial cardiovascular effects. The current safety trials and the non inferiority designs used to determine the CV outcomes relating to anti-diabetes medications are providing a pseudo blanket to our understanding of the CV effects of the newer agents and pose significant cost and conduct challenges. Future trials should be designed keeping in mind that the primary reason of developing newer agents is to have more effect on glucose lowering and the drugs should be judged based on its ability to influence multidimensional clinical outcomes. The studies should be robust and stratified which takes into account geographical differences and variations in background and ancillary therapy and their adverse effect profile.The study designs should be more adaptive and include head to head comparisons between newer novel agent and established existing treatments with extended follow up periods for better characterization and to evaluate the time dependent risk-benefit profile. Finally, the regulatory bodies should a have rethink on their strategy for drug approval relating to type 2 diabetes as the current trials are enormously costly and consuming huge amount of resources which may pose a major risk to future anti diabetes drug development

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