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Molecular Basis of Pathogenesis of Ectopic Fat Deposition in DM2 – An Overview

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

The presence of fat, beyond physiological limits, in organs, other than the adipose tissue, like the liver, the skeletal muscle, the heart and the pancreas etc is called ectopic fat. It causes specific organ dysfunction in the tissues concerned. The importance of the ectopic fat is that it is connected to peripheral tissue insulin resistance, obesity, metabolic syndrome etc. Though the molecular mechanisms underlying the specific organ dysfunctions are understood, still grey areas exists as to the source of the ectopic fat and how it finds it's way to the specific sites of the target organs (intra-myocellular in skeletal muscle, hepatocyte cytoplasm of liver, epicardial surface and coronary arteries of heart etc.). The molecular mechanisms involving the actual ectopic deposition fat, are not clear. This article focuses on some of the grey areas in the pathogenesis of the ectopic fat deposition, besides reviewing briefly the facts already known in the literature about ectopic fat deposition.

Keywords: Ectopic fat; insulin resistance; acyl transferase; non alcoholic fatty liver; beta cell dysfunction of pancreas; fatty acid transporters; lipolysis; Triglyceride synthesis.

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1. INTRODUCTION

The storage of fat in organs other than the adipocyte, like skeletal muscle, the liver, the heart and the pancreas etc. Is called ectopic fat deposition. This is pathological and causes the dysfunction of the organ concerned. Ectopic fat is linked to IR (insulin resistance), met's (metabolic syndrome) obesity and DM2 (diabetes mellatus type 2 [1]. Age, sex, ethnicity, macronutrient composition of the diet, gut microbial composition, epigenetics, genetics, metabolic inflexibility are suggested to play an important role in ectopic fat accumulation. Even the possibility of a specific phenotype is suggested [2]. The matter of ectopic fat continues to attract the attention in the literature. However, certain grey areas exist in the pathogenesis of ectopic fat deposition. There is consensus as to the nature of ectopic fat being the triglyceride, but not about what the source of this TAG is and what fatty acids make up the ectopic TAG. As regards the sources of the ectopic fat is concerned the excess fatty acids left in the cytosol of the mitochondria, beyond it's oxidative capacity, is favoured. The other possible sources like the adipose tissue, liver and the intestine (dietary fat). The fatty acid part of the TAG (trial glycerol) is believed to be LCFA (long chain fatty acid), but which LCFA is not identified. But certain biomarkers are identified, which throw light as to their source. PUFA (poly unsaturated fatty acid) like EPA (Eicosapentaenoic acid) and DHA (docosahexaenoic acid) and essential FAs like alfa – linolenic (an omega-3 fatty acid) and linoleic acid (an omega-6 fatty acid) are considered good biomarkers for FAs of exogenous origin. SFA (saturated fatty acid) like palmate acid is considered a good biomarkers for endogenous (denovo fat synthesis) origin. Among people with obesity, serum ganglioside C22:0 and lactosylceramide C14:0 predicted muscle TAG. [3] It is also not decided as to whether the TAG is locally synthesised or brought from an extensive source. In either case, the molecular mechanisms involved in the synthesis of TAG at the ectopic sites are not clearly elucidated. Thus, the information in the literature has certain lacuna. On the other hand, the molecular mechanisms involving the target organs dysfunction due to ectopic fat deposition are elucidated with respect to liver and muscle in, but the stand on pancreas is not yet clear. These matters are reviewed in the discussion below, in this article, particularly in the context of DM 2 and known molecular mechanisms are recapitulated.

The investigations used by several investigators to identify the ectopic fat are summarised in Table 1. [H]MRS is Considered the most sensitive test for measurement of fat in the liver and skeletal muscle in DM 2. Others have varying sensitivity and convenience.

Table 1. Investigations used in detecting ectopic fat

MRI
H- MRS.
CT scan.
Ultra sound
Biopsy.
Radio tagging of FA
liquid chromatography
Tandem mass spectroscopy).

2. DISCUSSION

2.1 Adipocyte, as a Source of the Ectopic Fat and Adipocyte Dysfunction as a Means of Ectopic Fat Deposition

It is reasonable to assume Adipocyte as the source of the ectopic fat, as it is the largest and permanent store of fat. Though fat may be detected physiologically in, say muscle, during sustained muscular exercise, it is meant to meet the extra demands for energy. In other words, any fat stored in target organs is meant for physiological purpose and is only a temporary or time being store. Ectopic fat on the other hand is definitely pathological. The intra myocellular accumulation of fat in an insulin resistant DM2 patient is an example of pathological fat deposit. Fat is mobilised from the Adipocyte by way of lipolysis, under the inflence of HSL (hormone sensitive lipase). The HSL is thought to be regulated by glucagon previously, but current opinion is that insulin is the regulator "by cutting off the inhibitory brakes" on the enzyme. The lipolysis results in release of FFA and glycerol into circulation. FFA are directed to oxidative machinery of the cell mitochondria, while the glycerol is recycled to liver. This is what happens under physiological conditions. In conditions associated with IR like DM 2, adipose dysfunction leads to pathological responses. First of the pathological changes to occur are Adipocyte hypertrophy. This leads to compromised vascular supply and is chemical oxidative stress that opens stress signal pathways. Additionally ER (endoplasmic reticulum) stress either induced by hypoxia or excess nutritional intake. ER (endoplasmic

reticulum) stress predisposes to UPR. UPR induces stress signals, resulting in production of inflammatory cytokine and adiponectin. The distressed adipocyte, in addition, recruits macrophages and other immune cells. By positive feedback these recruit more immune cells. A chronic inflammatory state in the adipocyte is thus setup in adipocyte . The inflammation is systematised leading to peripheral IR. The adipocyte dysfunction increases lipolysis. More FFA (free fatty acid) flux is directed against the target organs with B - oxidative machinery. The increased flux to get her with mitochondrial dysfunction creates imbalance between the oxidative capacity of the mitochondria and the nutrient supply. The excess FFA find their way to the target sites as ectopic fact.

2.2 Mitochondrial as the Source and It's Dysfunction as Mechanism of Ectopic Fat Deposition

This view emphasises the break down of B-oxidative machinery, consequent to mitochondrial dysfunction. It is not intended to delve about how mitochondrial dysfunction occurs. A mismatch is created between FAS arriving in the cytosol from the ribosomes and the fraction that could by oxidised by the mitochondria. The FA thus left over in cytosol is deposited as ectopic fat in the muscles and liver etc. It may be recalled that the fatty acid product and released from FAS (fatty acid synthase) is palmitate (via the action of palmitoyl thioesterase) which is a 16:0 fatty acid (i.e. 16 carbons and no sites of unsaturation). Elongation of fatty acids occurs in the cytosol of the ribosomes. The FAs of C 16 ie palmate acid is released into the cytosol of mitochondria. The B - Oxidative machinery of the mitochondrial matrix reduce in 7 oxidative cycles reduce the 16 C FA to 2 C acetyl- Coa which enters the citric acid cycle and later into ETC (electron transport chain) to produce ATP. So it is imperative, if this view is accepted, the un-oxidised FA that is palmitic acid, the LCFA, is involved in the ectopic fat deposit. This fits with the agreed fact that ectopic fat contains is 16 C, palmate acid, which is to be verified experimentally that may lend credence to this view.

2.3 VLDL as Source of Ectopic Fat Deposit

The triglycerides absorbed and brought to the liver and the cholesterol synthesised in liver, are coated with a protein moiety and packed as small particles called VLDL (very low density lipoproteins Transfer of TG into lipoproteins involves the cotranslational addition of lipids to apolipoprotein B (apoB) in a process catalysed by the microsomal triglyceride transfer protein (MTP) (as reviewed in Refs. [4]. The VLDL, thus formed are released into the blood to be transported to the adipose tissue which are the storage sites of fat. The lipoprotein cover make the particle water soluble as the fats are hydrophobic and can not be carried as such in the blood stream. Thus VLDL is a rich source of dietary fats absorbed by intestine and processed by the liver. It is conceivable that, if the VLDL fails to make it into the adipocyte, the VLDL may be directed to the target organs of ectopic fat deposition. This makes the VLDL a potential candidate as to the source of ectopic fat. The salient aspects relevant to VLDL, in this context, are reviewed.

- Insulin resistance is associated with increased VLDL-Apo B production, principally in the VLDL 1 fraction [5,6]
- Hepatic insulin resistance would diminish any suppressive effect of insulin on VLDL production in insulin-resistant individuals.
- Insulin resistance of adipose tissue leads to higher circulating nonesterified fatty acid (NEFA) concentrations, and an increased fatty acid flux to the liver can stimulate VLDL production
- liver fat content correlates strongly with both hepatic VLDL1-apoB and VLDL1-triglyceride production rates
- Hyperinsulinemia could play a causal role in mediating hepatic steatosis through up-regulation of de novo lipogenesis [7] hyperinsulinemia could play a causal role in mediating hepatic steatosis through up-regulation of *de novo* lipogenesis
- IR subjects show higher skeletal muscle VLDL-TAG extraction than normal glucose tolerant (NGT) individuals.
- The dietary TG from chylomicrons and cholesterol are packed into VLDL and released into blood by the liver. Normally the LPL enzyme present in the luminal side of endothelial cells lining the capillaries of adipocyte hydrolyses the TAG while the cholesterol rich she'll of VLDL remains a VLDL remnant. Since LPL of adipose tissue is sensitive to insulin, in insulin resistant states, the VLDL remains in the blood contributing to high blood levels of VLDL. This leads to increased peripheral

distribution of VLDL leading to ectopic fat deposition.

2.4 Intestines as a Source of Ectopic Fat

The dietary TAG is hydrolysed first to diacyl glycerol (DAG) and mono acyl glycerol in the apical epithelium of the small intestine and resynthesized at the baso - lateral surface back to TAG which are then packed as chylomicrons. [8] Through lymphatic, the chylomicrons reach the liver. Later fate in the form of VLDL is already seen above. It may be noted the LPS hydrolyses some of the circulating chylomicrons to release TAG. Under physiological conditions, the amount of TAG so formed may be insignificant. But under conditions of excess dietary fat intake it makes significant contribution taking into the consideration, the other fact, that the LPL is unresponsive in in insulin resistant states like DM2.This results in the 'spill over' of TAG from the chylomicrons which may find their way into ectopic fat sites directly. Further LCFA fraction, which is considerable in amount in the fat rich diet may involve in the 'Chylomicron spill over' leading to its surfacing at the ectopic fat sites.

2.5 Are the TAGS Synthesised Locally in the Ectopic Sites or Deposited There from Their Source of Origin?

TAGs can not enter the cell as such, they are split into fatty acids and glycerol. These, on entering the cell again are synthesised to TAGs. The procedure is same whether it is adipocyte or myocyte, hepatocyte or cardiomyocyte. The difference is that adipose tissue is the single largest storage site of fats, in the form of TAG (an anabolic process). In tissues other than adipocyte the are mobilised from adipose tissue for their energy metabolism catabolism/ B-oxidation. Physiologically the stay in the ectopic tissue is transient, until it is metabolised. When fat remains without being metabolised it is pathological and is named as ectopic fat deposit. The other difference is that the adipocyte lacks glycerol kinase which phosphorylation the glycerol to active form, glyceraldehyde 3 phosphate. The later metabolite is obtained from DHAP (dihydroxy acetone phosphate) formed in the glycolysis pathway. But in insulin resistant states/ DM2, glycolysis is inhibited and hence the adipocyte is deprived of the necessary substrate for the TAG synthesis. Whereas muscle and liver capillaries have LPL in their liminal surface of the endothelium, capable of hydrolysis of TAG that reach these sites. Further unlike LPL of adipocyte which is sensitive to insulin, the LPL (lipoprotein lipase) in other tissues is not dependent on insulin, but are influenced by glucagon, the predominant harmony in insulin resistant states / DM2. The remaining glycerol from either lipolysis or VLDL (which fails to enter adipocyte in the absence of insulin is transported to the liver where the same is incorporated in the denovo synthesis of fat.

2.6 Role of Fat Transporters

These are transmembrane carrier proteins that help transport into the cell from the blood stream.[9]The key fatty acid transporters FAT/CD36 and FABPpm are expressed in muscle and heart and their plasma membrane content is positively correlated with rates of fatty acid transporters. FABP (fatty acid binding protein) are a family of about 9 intracellular proteins which help FA and other molecules across the cell membrane. FABP 1 is expressed in liver, FABP in intestine, 3 in skeletal muscle and FABP 4 in the adipose tissue HFABP, a separate entity apart from the group of 9 FABP, highly expressed in cardiac muscle .It is now considered a good biomarker of MI and has prognostic value also. The FAT / CD 36 is a key regulated of FA transport in skeletal muscle and heart. Insulin and muscle contraction stimulate it and translocation it from an intracellular depot to cell membrane. This explains how the ectopic fat in muscle under physiological conditions is metabolised during muscular exercise Evans also in IIR states/ DM2. In the liver , it is stimulated to 80% of its action by PPAR alfa but the later has no effect on skeletal muscle CD 36. It is believed to play a role in the transport of activated acyl groups across the outer mitochondrial membrane in B-Oxidation.

2.7 Synthesis of TAG in the Ectopic Sites – The Role of Acyl Transferase

Esterification of glycerol-3- phosphate with a long-chain acyl-CoA was the initial step in the synthesis of triacylglycerol (TAG) [10]. There are two isoforms, one located in the mitochondrial outer membrane and the other in the endoplasmic reticulum [11]. The endoplasmic reticulum (microsomal) activity was inhibited by sulfhydryl reagents such as *N*-ethylmaleimide (NEM) and exhibited no preference for particular acyl-CoA species, whereas the mitochondrial activity was resistant to NEM inactivation and preferred to use saturated acyl-CoAs like 16:0-CoA and 18:0-CoA [12].

First mammalian GPAT isoform cloned [13,14] resides in the outer mitochondrial membrane, is resistant NEM inactivation and prefers to use saturated acyl-CoAs [A second mitochondrial GPAT, GPAT2, also resides in the outer mitochondrial membrane, but its activity is inhibited by NEM and it has no long-chain acyl-CoA preference The NEM-sensitive endoplasmic reticulum isoforms, GPAT3 and GPAT4, were identified very recently [15,16,17].

GPAT1 activity is highest in rat liver and adipose, tissues with a high capacity for TAG synthesis regulation of *Gpat1* by insulin is mediated by sterol regulatory element binding protein-1 (SREBP-1), a transcription factor responsible for activating numerous genes required for enhanced fatty acid and TAG synthesis [18]. Since both insulin and SERBP-1 are inhibited in insulin resistance, they are not perhaps relevant to ectopic fat deposits GPAT2 has no preference for 16:0-CoA compared with oleoyl-CoA. *GAPT 2* mRNA transcript was highly abundant in testis and relatively low in other tissues

It is believed to have minor role in TAG synthesis the significance of its occurrence in abundance in testis is not known. microsomal GPAT activity seemed to be less influenced by hormonal and nutritional status than GPAT 1.

In adipose tissue however, other studies showed inactivation of microsomal GPAT activity by a tyrosine kinase and activation by insulin or sodium orthovanadate is highly expressed in epididymal adipose tissue as well as small intestine in mice, and in kidney, testis, heart, skeletal muscle, and thyroid in humans. GPAT 4 can use a range of acyl-CoA substrates from 12 to 20 carbons, however the highest GPAT activity occurs with acyl-CoA species of 16- and 18-carbons, regardless of the level of saturation. Consistent with GPAT's role in initiating TAG synthesis, *Gpat4* mRNA is highly expressed in mouse lipogenic tissues, including liver and both BAT and visceral white adipose tissues, including omental, epididymal, and retroperitoneal depots. *Gpat4* mRNA is also highly expressed in mouse testis [19] GPAT4 *in vivo* normally initiates the synthesis of TAG the individual GPAT isoforms may generate distinct lipid intermediates destined for specific biosynthetic pathways.

Step 1 : G3P is esterified to LPA (lysophosphatidic acid) by GPAT 3 & 4.

Step 2 : LPA(lysophosphatidic acid) is esterified to PA by 5 AGPATs (acyl glycerophosphate acyl transferees)

Step 3 : PA (phosphatidic acid) is hydrolysed to DAG by PAPASE (phosphatidic acid phosphatase, also called lipins 1 - 5.

Step 4 : DAG (Diacyl glycerol) is esterified to TAG (triacyl glycerol) by DGAT 1 & 2.

The lipin-1 has a dual role in that it operates in collaboration with known nuclear receptors as a transcriptional coactivator to modulate lipid metabolism (lapin 1α) while lipin 1β is associated with induction of lipogenic genes such as fatty acid synthase, stearoyl CoA desaturase and DGAT. Abnormalities in lipin-1 expression are known to be involved in some human disease states that may lead to the metabolic syndrome. Lapin 2 is a similar phosphatidate phosphor-hydrolase, which is present in liver and brain and is regulated dynamically by fasting and obesity (in mice), while lipin 3 is found in the gastrointestinal tract and liver.

2.8 Target Organs of Ectopic Fat and Organ Dysfunction

The target organs are skeletal muscle, liver, heart and pace as.

2.8.1 The liver

The cut-off value for fat in liver is 5% of the volume of liver or 5% of hepatocytes contain visible fat. (60). Above this value it is considered. NASH (non alcoholic steatohepatitis) which may progress to fibrosis and cirrhosis of the liver.

1) **Hepatic IR:** In the liver ectopic causes hepatic insulin resistance manifested by decreased uptake of glucose into hepatocyte and increased gluconeo-genesis.
2) **NAFLD & NASH:** Harmless accumulation of fat in liver without any evidence of inflammation and scarring, not due to alcohol is NAFLD.

With inflammation and scarring and progressing to the cirrhosis of liver and even carcinoma liver is called non alcoholic steato hepatitis (NASH)

Between 30 and 40 percent of adults in the United States have NAFLD. About 3 to 12 percent of adults in the United States have NASH.1

Researchers have found NAFLD in 40 to 80 percent of people who have type 2 diabetes and in 30 to 90 percent of people who are obese 2.

2.8.2 Molecular basis of NAFLD –NASH

The stages of NAFD are presented in Table 2 and the factors involved in the pathogenesis of NFLD in Table 3.

Table 2. Stages o-f NAFLD

Stage1-Simplefatty liver.
Stage2-NASH Non alcoholic steatohepatitis.
Stage3- Fibrosis
Stage 4- Cirrhosis of liver.

Table 3. The factors believed to be in involved in the pathogenesis

Liver inflammation6
Liver cells apoptosis
Oxidative stress
Mitochondrial inflammation and dysfunction.
Gut microbes.

2.8.3 The skeletal muscle

The predominant effect is insulin resistance and consequent reduced glucose uptake. Studies reported decreased mitochondrial function at normal IMCLs (intra-myocellular lipids) levels [20] suggesting that impaired mitochondrial function is not a prerequisite for IMCLs accumulation. Mitochondrial dysfunction, on the other hand is thought the due to lipid peroxides formation due to defective oxidation of fats. It was reported that SFA preferentially accumulate as DAG in skeletal muscle and may thereby potentially interfere with insulin signalling, whereas MUFA and PUFA more readily convert to TAG [19].

Further the glucose and insulin responses to a high SFA meal was greater when compared to a high PUFA meal in IR men, indicating an impaired postprandial insulin sensitivity, which was accompanied by a decreased skeletal muscle lipid turnover and FSR of TAG and DAG after the high SFA meal [20].

2.8.4 The heart

One newly appreciated contributor is the angiogenic capability of SAT. Recent work has shown that, in general, SAT has a higher ability than VAT to expand its capillary network. Epiicardial adipose tissue (EAT) adiposity is linked to and CAD risks [21] the ectopic fat is epicardia or intramuscular. It is estimated that among people with NAFLD, heart disease is the top killer, accounting for more than 25% of deaths. It causes

- Diastolic dysfunction.
- Cardiomyopathy.
- Heart failure.
- Atherosclerosis of coronary arteries.
- Myocardial infarction.

2.8.5 The Pancreas

The circulating TAG and HbA1C are the best biomarkers for pancreatic fat [22]

The matter is not clear with the pancreas. The following effects of ectopic fats are suggested.

- Decreased glucose stimulated insulin secretion,
- Decreased expression of genes
- Possibly B – cell dysfunction. All these Together, it is called as lipotoxicity.

2.8.6 Insulin resistance- pathway in liver, skeletal muscle and the heart

similar to that described for skeletal muscle .The Increased supply of LCFA, over and above the oxidative capacity of the mitochondria due to mitochondrial dysfunction causing impairment in β-oxidation exist, LC-CoA accumulates and is broken down to intermediates like DAG and ceramide. These intermediary fatty acid meta-bolites induce activation protein kinase C (PKC) isoforms, IKB-kinase-β and Jun N-terminal kinase, which phosphorylate insulin-receptor substrate (IRS) 1 [23]. Phosphorylated IRS 1 can't activate phosphatidyl-inositol-3-kinase (PI3K), resulting in a decreased glucose transporter 4 (GLUT4) regulated glucose transport over the cell membrane. The result is the reduced glucose uptake by the cell and consequent hyperglycaemia.

The reduced activity of AKT2, a protein kinase downstream of IRS and PI3K, results in decreased phosphorylation of the forkhead box O (FOXO) transcription factor, allowing it to enter the nucleus and activate the transcription of the rate-controlling enzymes of gluconeogenesis. The result is increased hepatic glucose production and decreased hepatic glucose uptake, which both contribute to increased plasma glucose levels.

2.8.7 Physiological vs pathological intramyocellular lipid accumulation

Intramyocellular lipid collection can be physiological or pathological, a distinction which

is often necessary [25]. In endurance-trained athletes IMCLs (intra myocellular lipids) are an adaptive response, the IMCLs serve as a readily available energy source. In these athletes, IMCLs are not deleterious because of the increased capacity to oxidize lipids. In insulin-resistant T2DM patients, the increased IMCLs stores are the result of increased FFA availability and impaired fatty acid oxidation [25]. The latter leads to accumulation of lipid intermediates with the ascribed toxic effects on insulin signalling.

The cut-off value for abnormal lipid accumulation in the liver has been defined as more than 5% of liver volume or when more than 5% of hepatocytes contain visible intracellular lipids. Fat content above this limit cause NAHS which may progress to NASH, fibrosis and cirrhosis.

2.8.8 The author's summing up

How the glucose metabolism is blocked and B-Oxidation of fats emerges as alternative source of energy in DM 2 has been elucidated by this author [26].IIt was also proposed by this author that the blockage of glycolytic pathway at the level of FBF results in opening of HMP shunt [27]. Due to the absence of glycerol kinase (GK) in the adipose tissue. Glycerol moiety for adipose tissue comes from DPHA from glycolysis under physiological conditions and is converted to GD3P.

2.8.9 DHAP pathway

The dihydroxyacetone-phosphate in peroxi-somes or endoplasmic reticulum can be acylated by a specific acyltransferase to form 1-acyl dihydroxyacetone-phosphate, which is reduced by dihydroxyacetone-phosphate oxido-reductase to lysophosphatidic acid, which can then enter the Kennedy pathway described under discussion and summarised below) to triacylgly-cerols .

2.8.10 The kennedy pathway

SF Yet, S Lee, YT Hahm, HS Sul Expression and identification of p90 as the murine mitochondrial glycerol-3-phosphate acyltransferase.

But in other tissues like liver and muscle, where the GK is available, it phosphorylates glycerol to G3DP. This step is essential for the synthesis of Triglycerides by liver, muscle and adipose tissue. In DM2 since glycolytic pathway is shut down, the adipose tissue gets G3DP from the HMP shunt. The FFA from diet are transported into the adipose tissue by fatty acid transporters and by perhaps free diffusion. The triacyl glycerol (TAG) synthesis in occurs via Kennedy pathway or glycerophosphate pathway as outlined above. The FA from chylomicrons and VLDL cannot enter through the adipocyte because the LPL is insulin sensitive and the hormone is ineffective in DM2 (Due to IR). So the VLDL/chylomicrons are directed towards peripheral tissues (like liver and skeletal muscle). The FFA are transported into the cell of the target organs of ectopic transport by fatty acid transporters described already.

The FA from increased lypolysis are esterified with glycerol resulting in TG synthesis in the peripheral tissues. Unlike in physiological conditions such as fasting, starvation etc where B-Oxidation is interrupted by feeding or refeeding which replenish the depleted TG source, In DM2, continuous replenishment of FA pool is essential to sustain fuel for the B-oxidation. Since the denovo synthesis of fat is defective in DM2, replenishment of FA comes from dietary pool. If it were to come from denovo synthesis of FA, the lipogenesis should occur by stimulation of melon Coa. Both B oxidation and lipogenesis cannot occur simultaneously as it results in a futile cycle. This would perhaps never occurs.

Insulin lack increases lypolysis, which results in hydrolysis of TG into FFA and TG are released into the blood. FFA that reaches the Mitochondria serves as a substrate for the continued B- oxidation of fats. FA in excess of metabolic needs from lipolysis are taken up by acyl transferase in the endothelial cells of capillaries of skeletal muscle and liver. The triglyceride synthesis in the ectopic sites occurs by MG pathway (monoacylglycerol pathway).

2.8.11 The MG pathway

MG pathway is found in specific cell types, such as enterocytes, hepatocytes, and adipocytes, where it may participate in the reesterification of hydrolysed to TG. The monoacylglycerols are first acylated by an acyl coenzyme monoacylglycerol acyltransferase with formation of sn-1,2-diacylglycerols mainly as the first intermediate in the process. Monoacylglycerols can also be synthesised by the acylation of glycerol and these can also be acylated by DGAT1. There are three isoforms of the monoacylglycerol acyltransferase in humans of which MGAT2 is most active in the intestines and liver and MGAT1 in adipose tissue. Finally, the acyl coenzyme, diacylglycerol acyltransferase (DGAT1) reacts with the sn-1,2-diacylglycerols only to form triacylglycerols.

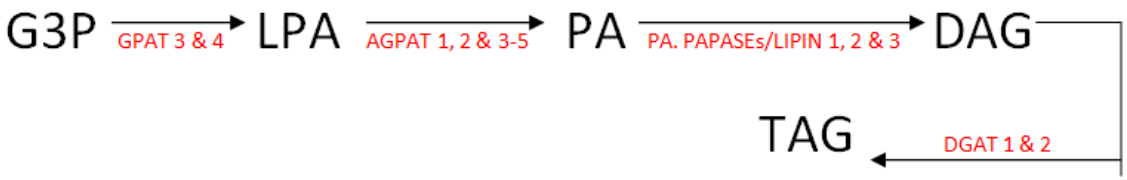

Fig. 1. The kennedy path way

G3P – glyceraldehyde 3 phosphate ; LPA – lysophosphatidic acid, PA – phosphatidic acid , DAG- Diacyl glycerol , TAG- Triacylglycerols glycerol (DGAT) diacylglycerol acyl transferase , GPAT – Glyceraldehyde phosphate acyl transferase . PAPASE- phosphatidic acid phosphatase , AGPATs - acyl glycerophosphate acyl transferees

The same events repeat in case of VLDL which fail to enter adipocyte (as LPL is insulin sensitive and there is relative deficiency of insulin in DM 2).

The LPL of the peripheral tissue is glucogon sensitive (the predominant harmony in DM2/ IR states) which hydrolyses the VLDL. The rest of the TG synthesis in liver and muscle is same as in case of FA from increased lipolysis from adipocyte.

As regarding the view that the LCFA remaining in the cytosol and diffusing into the inter-cellular space as in skeletal muscle when it load exceeds the oxidising capacity of the mitochondria, though favoured by some, may not contribute to ectopic fat deposition in the author's view as explained below. The LCFA that enter mitochondrial cytosol are distained for B -oxidation, sustaining of which is essential tor the energy metabolism as in DM2. The CPT 1 enzyme which is considered the rate limiting step in B-Oxidation is stimulated by PPAR alfa which acts as a sensor of energy metabolism. The LCFA that are the ligands of PPAR alfa and mediates effect on CPT 1(and also CPT 2).The probability of the LCFA reaching cytosol in excess of B -oxidative capacity of the mitochondria, is less than mitochondrial dysfunction causing CAPACITY CPT 1 to recruit LCFA from cytosol into mitochondria. Such a happening is possible in DM2 due to oxidative stress / increased production of the free radicals in DM 2. The CPT 1 being rate limiting, the slowed rate or the enzyme may create a back log in the cytosol. But as the LCFA act as ligands for PPAR alfa its energy sensor function, the reduced activity would send negative feed back signals to PPAR alfa where by further dumping of LCFA into the cytosol of the mitochondria is stopped. Since it is inconceivable that CPT 1 would come to a grinding halt due to oxidative stress, given time the slowed enzyme clears the backlog of LCFA in the cytosol.

When the cytosol load of LCFA is cleared, the inhibitory regulation of CPT 1 on PPAR alfa, ceases and its stimulating effect on CPT 1 comes to the fore, to continue B -oxidation uninterrupted. So in the author's view the LCFA backlog created in cytosol is not disposed Into the ectopic fat as conceived by the prevailing speculation but is used for the purpose for which it is transported into the cytosol of mitochondria but at a lesser speed should mitochondrial dysfunction develop in the course of DM2.

3. CONCLUSION

The article briefly reviewed the various concepts regarding ectopic fat deposition. Recent information on the subject visit a visit each cocept is updated. Though, mitochondrial dysfunction theory is much favoured, the author feels that dietary origin of fat has more say in deciding ectopic fat deposition.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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