

## A Cholesterol and Actinide Dependent Shadow Biosphere of Archaea and Viroids in Metabolic Syndrome X

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### Abstract

**Objective:** Endogenous digoxin has been related to the pathogenesis of type 2 diabetes mellitus, coronary artery disease and cerebrovascular disease. Elevated digoxin levels are described in endomyocardial fibrosis and root wilt disease of coconut seen in same endemic zones with phytoplasm, rutile and viroids important in their pathogenesis. The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered.

**Research design and methods:** 10 cases each of type 2 diabetes mellitus, coronary artery disease- acute coronary syndrome and acute cerebrovascular thrombosis before starting treatment and 10 age and sex matched healthy controls from general population were chosen for the study. The CAD and CVA patients were non-diabetics. Cholesterol substrate was added to the plasma of the patients and the generation of cytochrome F420, free RNA, free DNA, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids were studied. The changes with the addition of antibiotics and rutile to the patient's plasma were also studied. The statistical analysis was done by ANOVA.

**Results:** The parameters mentioned above were increased the patient's plasma with addition of cholesterol substrate. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of rutile

increased their levels.

**Conclusions:** An actinide dependent shadow biosphere of archaea and viroids is described in type 2 diabetes mellitus, coronary artery disease- acute coronary syndrome and acute cerebrovascular thrombosis contributing to their pathogenesis.

**Abbreviations:** EMF- Endomyocardial fibrosis; PAH- Polycyclic aromatic hydrocarbons; HERV- Human endogenous retroviruses; GABA- Gamma aminobutyric acid; DXP- D-xylulose phosphate; GPCR- G-protein coupled receptor; TNF alpha- Tumour necrosis factor alpha; TLR- Toll receptor

**Key words:** Coronary artery disease; Cerebrovascular disease; Type 2 diabetes mellitus; Archaea; Viroids; Cholesterol; Actinide

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### INTRODUCTION

The human body synthesises an endogenous sodium-potassium ATPase inhibitor digoxin which plays a role in neuro-immuno-endocrine integration as well as in cardiovascular/ metabolic disorders. Endomyocardial fibrosis (EMF) along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like rutile producing intracellular magnesium deficiency due to rutile-magnesium exchange sites in the cell membrane has been implicated in the etiology of EMF<sup>[1]</sup>. Endogenous digoxin, a steroidal glycoside which functions as a membrane sodium-potassium ATPase inhibitor has also been related to its etiology due to the intracellular magnesium deficiency

it produces<sup>[2]</sup>. Organisms like phytoplasmas and viroids have also been demonstrated to play a role in the etiology of these diseases<sup>[3,4]</sup>. Endogenous digoxin has been related to the pathogenesis of type 2 diabetes mellitus, coronary artery disease and cerebrovascular disease<sup>[2]</sup>. The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered<sup>[5,6,7]</sup>. Davies has put forward the concept of a shadow biosphere of organisms with alternate biochemistry present in earth itself<sup>8</sup>. An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described<sup>6</sup>. The intracellular endosymbionts archaea and their intron derived viroids constitute the third element regulating the human body.

## MATERIALS AND METHODS

Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The following groups were included in the study:- type 2 diabetes mellitus, coronary artery disease- acute coronary syndrome and acute cerebrovascular thrombotic stroke. The coronary artery disease and cerebrovascular disease patients chosen for the study did not have type 2 diabetes mellitus as a risk factor. There were 10 patients in each group and each patient had an age and sex matched healthy control selected randomly from the general population. The blood samples were drawn in the fasting state before treatment was initiated. Plasma from fasting heparinised blood was used and the experimental protocol was as follows (I) Plasma+phosphate buffered saline, (II) same as I+cholesterol substrate, (III) same as II+rutile 0.1 mg/ml, (IV) same as II+ciprofloxacin and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond<sup>[9]</sup>. Aliquots were

withdrawn at zero time immediately after mixing and after incubation at 37°C for 1 hour. The following estimations were carried out:- Cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids<sup>[10,11,12,13]</sup>. Cytochrome F420 was estimated fluorimetrically (excitation wavelength 420 nm and emission wavelength 520 nm). Polycyclic aromatic hydrocarbon was estimated by measuring hydrogen peroxide liberated by using glucose reagent. The statistical analysis was done by ANOVA.

## RESULTS

The parameters checked as indicated above were:- cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids. Plasma of control subjects showed increased levels of the above mentioned parameters with after incubation for 1 hour and addition of cholesterol substrate resulted in still further significant increase in these parameters. The plasma of patients showed similar results but the extent of increase was more. The addition of antibiotics to the control plasma caused a decrease in all the parameters while addition of rutile increased their levels. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of rutile increased their levels but the extent of change was more in patient's sera as compared to controls. The results are expressed in tables 1-7 as percentage change in the parameters after 1 hour incubation as compared to the values at zero time.

**Table 1**  
**Effect of Rutile and Antibiotics on Muramic Acid and Cytochrome F420**

Group	ATP synthase % (Increase with Rutile)		ATP synthase % (Decrease with Doxy)		CYT F420 % (Increase with Rutile)		CYT F420 % (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.41	0.15	18.63	0.12	4.48	0.15	18.24	0.66
DM	24.10	1.61	65.78	4.43	22.59	1.86	57.05	8.45
CAD	23.34	1.75	66.80	3.43	22.76	2.26	60.49	6.86
CVA	22.94	1.99	68.30	2.52	21.01	2.29	62.37	8.01
F value	403.394		680.284		306.749		130.054	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 2**  
**Effect of Rutile and Antibiotics on Free DNA and RNA**

Group	DNA % change (Increase with Rutile)		DNA % change (Decrease with Doxy)		RNA % change (Increase with Rutile)		RNA % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.37	0.15	18.39	0.38	4.37	0.13	18.38	0.48
DM	23.01	1.67	65.35	3.56	23.33	1.86	66.46	3.65
CAD	23.12	1.71	65.12	5.58	24.01	1.17	66.66	3.84
CVA	22.51	1.85	63.56	5.29	22.95	1.90	66.39	3.83
F value	337.577		356.621		427.828		654.453	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 3**  
**Effect of Rutile and Antibiotics on HMG CoA Reductase and PAH**

Group	HMG CoA R % change (Increase with Rutile)		HMG CoA R % change (Decrease with Doxy)		PAH % change (Increase with Rutile)		PAH % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.30	0.20	18.35	0.35	4.45	0.14	18.25	0.72
DM	23.06	1.65	62.25	6.24	23.40	1.55	65.77	5.27
CAD	23.63	1.58	61.19	7.03	22.22	2.33	61.73	6.33
CVA	22.51	2.47	60.77	5.89	23.87	1.64	66.01	5.78
F value	319.332		199.553		391.318		257.996	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 4**  
**Effect of Rutile and Antibiotics on Digoxin and Bile Acids**

Group	Digoxin (ng/ml) (Increase with Rutile)		Digoxin (ng/ml) (Decrease with Doxy+Cipro)		Bile acids % change (Increase with Rutile)		Bile acids % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	0.11	0.00	0.054	0.003	4.29	0.18	18.15	0.58
DM	0.47	0.04	0.202	0.025	22.87	2.58	64.51	5.93
CAD	0.49	0.07	0.202	0.021	22.22	2.44	63.47	6.98
CVA	0.51	0.07	0.195	0.023	22.33	2.18	62.20	6.33
F value	135.116		71.706		290.441		203.651	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 5**  
**Effect of Rutile and Antibiotics on Pyruvate and Hexokinase**

Group	Pyruvate % change (Increase with Rutile)		Pyruvate % change (Decrease with Doxy)		Hexokinase % change (Increase with Rutile)		Hexokinase % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.34	0.21	18.43	0.82	4.21	0.16	18.56	0.76
DM	20.67	1.38	58.75	8.12	23.23	1.88	65.11	5.14
CAD	20.16	1.07	57.08	9.83	21.88	2.11	65.02	4.40
CVA	20.60	1.81	58.97	7.03	21.98	2.12	65.78	6.08
F value	321.255		115.242		292.065		317.966	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 6**  
**Effect of Rutile and Antibiotics on ATP Synthase and Hydrogen Peroxide**

Group	ATP synthase % (Increase with Rutile)		ATP synthase % (Decrease with Doxy)		H <sub>2</sub> O <sub>2</sub> % (Increase with Rutile)		H <sub>2</sub> O <sub>2</sub> % (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.40	0.11	18.78	0.11	4.43	0.19	18.13	0.63
DM	23.72	1.73	66.25	3.69	23.27	1.53	58.91	6.09
CAD	23.78	1.20	66.90	4.10	23.24	1.85	57.08	7.42
CVA	23.47	1.60	66.27	3.88	23.32	1.60	61.45	7.01
F value	449.503		673.081		380.721		171.228	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 7**  
**Effect of Rutile and Antibiotics on Serotonin and Delta Amino Levulinic Acid**

Group	5 HT % (Increase with Rutile)		5 HT % (Decrease with Doxy)		PORPHYRIN % (Increase with Rutile)		PORPHYRIN % (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.34	0.15	18.24	0.37	4.40	0.10	18.48	0.39
DM	22.73	2.46	65.87	4.35	22.87	1.84	66.31	3.68
CAD	22.42	1.99	61.14	3.47	23.81	1.90	66.95	3.67
CVA	23.35	1.83	63.73	6.52	23.73	1.70	66.44	3.92
F value	348.867		364.999		372.716		556.411	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Abbreviations:

DM: Type 2 diabetes mellitus

CAD: Coronary artery disease

CVA: Cerebrovascular thrombosis

## DISCUSSION

There was increase in cytochrome F420 indicating archaeal growth in type 2 diabetes mellitus, coronary artery disease and cerebrovascular disease. The archaea can synthesise and use cholesterol as a carbon and energy source<sup>[14,15]</sup>. The archaeal origin of the enzyme activities was indicated by antibiotic induced suppression. The study indicates the presence of actinide based archaea with an alternate actinide based enzymes or metalloenzymes in the system as indicated by rutile induced increase in enzyme activities<sup>[16]</sup>. There was also an increase in archaeal HMG CoA reductase activity indicating increased cholesterol synthesis by the archaeal mevalonate pathway. The archaeal beta hydroxyl steroid dehydrogenase activity indicating digoxin synthesis and archaeal cholesterol hydroxylase activity indicating bile acid synthesis were increased<sup>[17]</sup>. The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate and hydrogen peroxide<sup>[15]</sup>. The pyruvate gets converted to glutamate and ammonia by the GABA shunt pathway. The archaeal aromatization of cholesterol generating PAH, serotonin and dopamine was also detected<sup>[17]</sup>. The archaeal glycolytic hexokinase activity and archaeal extracellular ATP synthase activity were increased. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms<sup>[18]</sup>. There was an increase in free RNA indicating self replicating RNA viroids and free DNA indicating generation of viroid

complementary DNA strands by archaeal reverse transcriptase activity. The actinides modulate RNA folding and catalyse its ribozymal action. Digoxin can cut and paste the viroidal strands by modulating RNA splicing generating RNA viroidal diversity. The viroids are probably escaped archaeal group I introns which have retrotransposition and self splicing qualities<sup>19</sup>. The decrease in free self replicating RNA and DNA with the addition of antibiotics indicates that the RNA viroids are derived from archaeal introns. Archaeal pyruvate can produce histone deacetylase inhibition resulting in endogenous retroviral (HERV) reverse transcriptase and integrase expression. This can integrate the RNA viroidal complementary DNA into the noncoding region of eukaryotic non coding DNA using HERV integrase as has been described for borna and ebola viruses<sup>[20]</sup>. The noncoding DNA is lengthened by integrating RNA viroidal complementary DNA with the integration going on as a continuing event. The archaea genome can also get integrated into human genome using integrase as has been described for trypanosomes<sup>[21]</sup>. The integrated viroids and archaea can undergo vertical transmission and can exist as genomic parasites<sup>[20,21]</sup>. This increases the length and alters the grammar of the noncoding region producing memes or memory of acquired characters<sup>[22]</sup>. The viroidal complementary DNA can function as jumping genes producing a dynamic genome and changing DNA sequences. The type 2 diabetes mellitus has been related

to altered genomic sequences mediated by HERV jumping genes. HERV particles have been related to the etiology of type 1 diabetes mellitus an autoimmune disease. The RNA viroids can regulate mRNA function by RNA interference<sup>[19]</sup>. The phenomena of RNA interference can modulate euchromatin/ heterochromatin expression. RNA viroidal mRNA interference plays a role in the pathogenesis of type 2 diabetes mellitus, coronary artery disease and cerebrovascular disease. Viroidal RNA mediated mRNA interference can modulate lipid metabolism triggering of dyslipidemias important in atherogenesis. The viroidal RNA modulation of T cell and B cell function by mRNA interference can lead to immune activation. Monocytic infiltration of the vascular wall is important in atherogenesis. Insulin resistance due to TNF alpha modulation of the insulin receptor can contribute to type 2 diabetes mellitus. The viroidal RNA mediated mRNA interference can also modulate insulin signalling and secretion leading onto type 2 diabetes mellitus.

The presence of muramic acid, HMG CoA reductase and cholesterol oxidase activity inhibited by antibiotics indicates the presence of bacteria with mevalonate pathway. The bacterial with mevalonate pathway include streptococcus, staphylococcus, actinomycetes, listeria, coxiella and borrelia<sup>[23]</sup>. The bacteria and archaea with mevalonate pathway and cholesterol catabolism had a evolutionarily advantage and constitutes the isoprenoidal clade organism with the archaea evolving into mevalonate pathway gram positive and gram negative organism through horizontal gene transfer of viroidal and virus genes<sup>[24]</sup>. The isoprenoidal clade prokaryotes develop into other groups of prokaryotes via viroidal/virus as well as eukaryotic horizontal gene transfer producing bacterial speciation<sup>[25]</sup>. The RNA viroids and its complementary DNA developed into cholesterol enveloped RNA and DNA viruses like herpes, retrovirus, influenza virus, borna virus, cytomegalo virus and Ebstein Barr virus by recombining with eukaryotic and human genes resulting in viral speciation. Bacterial and viral species are ill defined and fuzzy with all of them forming one common genetic pool with frequent horizontal gene transfer and recombination. Thus the multi and unicellular eukaryote with its genes serves the purpose of prokaryotic and viral speciation. The multicellular eukaryote developed so that their endosymbiotic archaeal colonies could survive and forage better. The multicellular eukaryotes are like bacterial biofilms. The archaea and bacteria with a mevalonate pathway uses the extracellular RNA viroids and DNA viroids for quorum sensing and in the generation of symbiotic biofilm like structures which develop into multicellular eukaryotes<sup>[26,27]</sup>. The endosymbiotic archaea and bacteria with mevalonate pathway still uses the RNA viroids and DNA viroids for the regulation of multicellular eukaryote. Pollution is induced by the primitive nanoarchaea and mevalonate pathway bacteria synthesised PAH and methane leading on to redox

stress. Redox stress leads to sodium potassium ATPase inhibition, inward movement of plasma membrane cholesterol, defective SREBP sensing, increased cholesterol synthesis and nanoarchaeal/mevalonate pathway bacterial growth<sup>[28]</sup>. Redox stress leads on to viroidal and archaeal multiplication. Redox stress can also lead to HERV reverse transcriptase and integrase expression. The noncoding DNA is formed of integrating RNA viroidal complementary DNA and archaea with the integration going on as a continuing event. The archaeal pox like dsDNA virus forms evolutionarily the nucleus. The integrated viroidal, archaeal and mevalonate pathway bacterial sequences can undergo vertical transmission and can exist as genomic parasites. The genomic integrated archaea, mevalonate pathway bacteria and viroids form a genomic reserve of bacteria and viruses which can recombine with human and eukaryotic genes producing bacterial and viral speciation. Bacteria and viruses have been related to the pathogenesis of atherogenesis and type 2 diabetes mellitus. Archaea, chlamydia, rickettsia, mycoplasma, cytomegalovirus and herpes virus has been related to the etiology of atherosclerosis<sup>[29]</sup>. Type 2 diabetes mellitus is related to an acute phase response and TNF alpha mediated insulin resistance. Persistent bacterial and viroid symbiosis can lead to immune activation and TNF alpha mediated insulin resistance<sup>[30]</sup>. The change in the length and grammar of the noncoding region produces eukaryotic speciation and individuality<sup>[31]</sup>. Changes in the length of noncoding region especially human endogenous retroviruses can lead onto type 2 diabetes mellitus, coronary artery disease and cerebrovascular disease<sup>[32]</sup>. HERV sequences functioning as jumping genes can produce alteration in DNA sequences contributing to type 2 diabetes mellitus<sup>[32]</sup>. The viroid complementary DNA integrated into the genome can also function as jumping genes producing new genomic sequences leading onto type 2 diabetes mellitus. The integration of nanoarchaea, mevalonate pathway prokaryotes and viroids in to the eukaryotic and human genome produces a chimera which can multiply producing biofilm like multicellular structures having a mixed archaeal, viroidal, prokaryotic and eukaryotic characters which is a regression from the multicellular eukaryotic tissue. This results in a new metabolic and immune phenotype leading to human diseases like type 2 diabetes mellitus, coronary artery disease and cerebrovascular disease. The microchimeras formed can lead to atherogenesis and type 2 diabetes mellitus.

Archaea and RNA viroid can bind the TLR receptor induce NFKB producing immune activation and cytokine TNF alpha secretion. The archaeal DXP and mevalonate pathway metabolites can bind  $\gamma\delta$  TCR and digoxin induced calcium signaling can activate NFKB producing chronic immune activation<sup>[2,33]</sup>. The archaea and viroid induced chronic immune activation and generation of superantigens. Immune activation results in induction of

NADPH oxidase which generates hydrogen peroxide. Cholesterol oxidase activity also generates hydrogen peroxide. Hydrogen peroxide can increase protein tyrosine kinase activity and suppress protein phosphatase activity increasing insulin receptor function. Immune activated NOX and bacterial cholesterol oxidase can thus regulate insulin receptor function. Immune activation can also produce insulin resistance. TNF alpha produced by chronic immune activation can modulate the insulin receptor producing insulin resistance<sup>[30]</sup>. Chronic immune activation and cholesterol oxidase generated hydrogen peroxide can induce neutral sphingomyelinase generating ceramide producing insulin resistance<sup>34</sup>. Immune activation and NFKB induction can suppress the nuclear receptors LXR, PXR and FXR. LXR suppression by NFKB stimulates HMG CoA reductase activity and suppresses cholesterol<sup>[1]</sup> 7 alpha hydroxylase activity<sup>[35]</sup>. This stimulates cholesterol synthesis and inhibits its degradation via the bile acid pathway. PXR suppression by NFKB prevents cholesterol detoxification via the bile acid shunt pathway<sup>[36]</sup>. Thus LXR and PXR suppression by NFKB produces acute cholesterol toxicity. This NFKB induced suppression of LXR and PXR can contribute to increased lipid and cholesterol synthesis contributing to obesity. FXR suppression can also lead to insulin resistance, dyslipidemias and increased connective tissue MPS deposition in vessel wall and atherogenesis. The cholesterol toxicity can lead to lipoprotein and cholesterol uptake by monocytes in the vessel wall producing atherogenesis. The archaea and viroid induced chronic immune activation can lead to monocyte infiltration of the vessel wall. This sets the stage for the atherogenetic process<sup>[29]</sup>. The increased cholesterol synthesis is important in stimulating archaeal growth which uses cholesterol as a carbon and energy source. Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype<sup>[37]</sup>. The increased glycolytic hexokinase activity, decrease in blood ATP, leakage of cytochrome C, increase in serum pyruvate and decrease in acetyl CoA indicates the generation of the Warburg phenotype. There is induction of glycolysis, inhibition of PDH activity and mitochondrial dysfunction resulting in inefficient energetics. Inefficient energetics owing to the Warburg's phenotype can contribute to metabolic syndrome X. The accumulated pyruvate enters the gaba shunt pathway and is converted to citrate which is acted upon by citrate lyase and converted to acetyl CoA, used for cholesterol synthesis<sup>[37]</sup>. The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. Ammonia can stimulate membrane sodium-potassium ATPase increasing ATP utilisation, produce mitochondrial transmembrane potential changes and produce mitochondrial dysfunction important in type 2 diabetes mellitus. The increased cholesterol substrate also leads to increased archaeal growth and digoxin

synthesis due to metabolic channeling to the mevalonate pathway. Digoxin can produce sodium-potassium ATPase inhibition and inward movement of plasma membrane cholesterol. This produces defective SREBP sensing, increased HMG CoA reductase activity and cholesterol synthesis<sup>[28]</sup>. The digoxin induced inward movement of plasma membrane cholesterol can alter membrane cholesterol/sphingomyelin ratio producing modified lipid microdomains<sup>[38]</sup>. The digoxin induced lipid microdomain modulation can regulate the GPCR couple adrenaline, noradrenaline, glucagon and neuropeptide receptors as well as protein tyrosine kinase linked insulin receptor. The digoxin mediated inhibition of nuclear membrane sodium-potassium ATPase can modulate nuclear membrane lipid microdomains and steroidal/thyroxine DNA receptor function. Thus endogenous digoxin can modulate all the endocrine receptors by regulating lipid microdomains. Hyperdigoxinemia is important in the pathogenesis of atherogenesis and metabolic syndrome X. Digoxin induced sodium-potassium ATPase inhibition results in an ATP sparing effect<sup>[39]</sup>. Eighty percent of the ATP generated is used to run the sodium-potassium ATPase pump. The digoxin inhibition of the sodium-potassium ATPase spares this ATP which is then used for lipid synthesis. Thus endogenous digoxin and the shadow biosphere generated Warburg phenotype can produce increased lipid synthesis and obesity important in metabolic syndrome X. Fat fuels insulin resistance by binding to the toll receptor and producing immune activation and immune infiltration of the adipose tissue. Digoxin can also increase lymphocytic intracellular calcium which leads on to induction of NFKB and immune activation<sup>[2]</sup>. The archaeal cholesterol catabolism can deplete the lymphocytic cell membranes of cholesterol resulting in alteration of lymphocytic cell membrane microdomains related receptors producing immune activation. The archaeal bile acids are steroidal hormones<sup>40</sup>. The archaeal bile acids can bind GPCR and modulate D2 regulating the conversion of T4 to T3. T3 activates uncoupling proteins reducing redox stress. Bile acids can also activate NRF 1/2 inducing NQO1, GST, HOI reducing redox stress. Bile acids can bind FXR regulating insulin receptor sensitivity and bind PXR inducing the bile acid shunt pathway of cholesterol detoxification. Bile acids can bind macrophage GPCR and VDR producing immunosuppression and inhibiting NFKB. This helps to modulate the archaea and viroid induced chronic immune activation. Thus the archaeal bile acids have a role opposite to digoxin and help to increase insulin sensitivity. The archaea and viroids can regulate the nervous system including the NMDA synaptic transmission<sup>[2]</sup>. NMDA can be activated by digoxin induced calcium oscillations, PAH and viroid induced RNA interference<sup>[2]</sup>. The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate. Glutamatergic transmission can lead to immune activation, atherogenesis and increased insulin signalling/release. The archaeal

cholesterol aromatase can generate PAH17. The PAH can also lead to insulin resistance and atherogenesis. Particulate pollution has been related to metabolic syndrome X, type 2 diabetes mellitus and vascular thrombosis. The aromatase generated serotonin and dopamine can lead onto mood disorders common in type 2 diabetes mellitus. The increased cholesterol catabolism generated glutamate can lead onto NMDA excitotoxicity and archaea/viroids can lead onto reactive amyloid deposition important in the pathogenesis of alzheimer's disease common in type 2 diabetes mellitus. The Warburg phenotype can lead onto oncogenesis common in type 2 diabetes mellitus. The higher degree of integration of the archaea into the genome produces increased digoxin synthesis producing right hemispheric dominance and lesser degree producing left hemispheric dominance. Right hemispheric dominance can lead to type 2 diabetes mellitus and vascular thrombosis. Thus the actinide, viroid and mevalonate pathway bacteria induced metabolic, genetic, immune and neuronal transmission changes can lead onto metabolic syndrome X and atherogenesis.

An actinide dependent shadow biosphere of archaea and viroids is described in type 2 diabetes mellitus, coronary artery disease- acute coronary syndrome and acute cerebrovascular thrombosis contributing to their pathogenesis. The archaea secreted digoxin serves as a messenger regulating metabolic and endocrine systems.

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