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FAMILIAL HYPERCHOLESTEROLAEMIA

ABSTRACT

In view of the widespread incidence of cardiovascular disease in Britain, it appears that high-risk groups are more prevalent than at first suspected, with atherosclerosis being the greatest single cause of mortality in the developed world. The multifactorial nature of the disease involves a bewildering array of complex physiological and biochemical processes. Though a multidisciplinary approach may seem prudent in the face of such alarming statistics, it must be viewed in context with overall health status of the population and a clear emphasis should be placed on primary prevention strategies in addition to the adoption of healthier lifestyles.

Despite the diverse aetiology, Familial Hypercholesterolaemia (FH) still remains an important issue that receives significant attention from both allopathic and alternative approaches to treatment. Pharmacological actions of conventional drugs (statins) used in this condition has proved effective in controlling and maintaining acceptable levels of plasma [cholesterol] in severe cases. Equally however, garlic (*Allium sativum*) is proving its worth as a serious contender to statins in a culture that is rapidly embracing alternative therapies that are closer to Nature.

Though secondary intervention is absolutely necessary in severe cases of elevated plasma [cholesterol], much is to be gained from combining resources and establishing a closer alliance between orthodox and complementary or alternative practices to management of disease where 'prevention' may prove more successful than 'cure'.

Definition

Familial Hypercholesterolaemia (FH) is an inherited disorder of lipid metabolism. Genetic abnormalities give rise to breakdown of the usual mechanisms for food production, storage , transport or utilisation of cholesterol, triglycerides or lipoproteins. Table 1 sets out the various types of hypercholesterolaemia. (Adapted from Heller et al.,1987 and Rees & Williams, 1995).

TABLE 1: - Summary of hyperlipidaemia classification; underlying causes and main clinical features
(Adapted from Heller et al., 1987 and Rees & Williams, 1995)

Type	Lipoprotein	Lipid in Excess	Frequency in population	Comments of clinical importance
I	Chylomicrons	**Cholesterol** & Triglyceride	1 : 100 000	Lipoprotein Lipase deficiency or specific protein (Apo cII) deficiency
IIa	LDL	**Cholesterol**	Heterozygous Individuals ? 1 : 300	FH (Hypothyroidism) and Familial Hyperlipidaemia. LDL cell receptors may be deficient
IIb	LDL & VLDL	**Cholesterol** & Triglyceride	Homozygous Individuals 1 : 1 000 000	Familial combined hyperlipidaemia (nephrotic syndrome, diabetes, anorexia). Risk of accelerated atheroma formation & early devt of CHD
III	IDL* & beta VLDL	Triglyceride & **Cholesterol**	Gene 1 : 100 Disease 1 : 10000	Familial (hypothyroidism, diabetes, obesity). 'Broad Beta Disease'. VLDL catabolism defect. Another factor may be necessary for genetic defect to manifest clinically (eg diabetes, obesity, hypothyroidism)
IV	VLDL	Triglyceride	1 : 500	Familial combined hyperlipidaemia Familial hypertriglyceridaemia (diabetes, chronic renal failure). May cause abdominal pains or pancreatitis

V	Chylomicrons & VLDL	Triglyceride & **Cholesterol**	1 : 500	Familial hypertriglyceridaemia due to Apo cII deficiency (lipoprotein lipase deficiency) and VLDL overproduction

*** IDL = Intermediate Density Protein**

Cholesterol is one of the plasma lipids, the others being triglycerides, phospholipids and free fatty acids, though it is only cholesterol and triglycerides that are of major clinical significance relative to atherogenesis. (Price & Wilson, 1997). Due to the insolubility of these lipids in plasma, they are bound to proteins as a mechanism for serum transport. Of the four major classes of lipoproteins highlighted in Table 2 (Adapted from Heller et al., 1987 and Price & Wilson, 1997). LDL contains the highest concentration of cholesterol, whereas the chylomicrons and VLDL are the richest in triglyceride and HDL contains the largest proportion of protein. (Price & Wilson, 1997).

TABLE 2: – Types of lipids found in the body and their relative clinical importance *(Adapted from Heller et al., 1987 and Price & Wilson, 1997)*

Lipoprotein	Properties of Clinical Importance
Chylomicrons	Triglyceride-rich particles formed in the intestines from dietary fats
Very Low Density Lipoproteins (VLDL)	Transports endogenously produced triglycerides from the liver. Broken down peripherally into HDL and LDL
Low Density Lipoprotein (LDL)	Commonly referred to as the 'cholesterol transporter'. Consists of 20% protein and 80% lipid. Used by peripheral cells for cell membrane metabolism and energy requirements. Excess levels in plasma are significant in atheroma formation
High Density Lipoprotein (HDL)	Consists of 50% protein and 50% lipid. Formed in peripheral cells by the breakdown of chylomicrons. High levels are not associated with accelerated atheroma or CHD. Thought to confer protective mechanism in CAD (coronary artery disease). Conversely, low levels appear to be atherogenic (ie. encourage atheroma formation)

Varying proportions of lipid to protein four types of lipoproteins; the protein elements are referred to as apoproteins and labelled A – E. The important characteristics that relate to clinical practice have been highlighted in Table 2.

Lipid Transport in the Body

The association between serum cholesterol elevation and increased risk of premature and severe atherosclerosis is well established. In normal endogenous pathway of lipid metabolism, dietary fat and cholesterol are absorbed through the gut and assembled there as chylomicrons; the largest lipoprotein particle. Owing to their large molecular size, they prove too big to be usefully metabolised as their entry into cells is not possible. Therefore the protein component of chylomicrons (the **apoprotein**) activates the enzyme **lipoprotein lipase** which catalyses its breakdown in the capillary walls of fatty and muscle tissue into free fatty acids and monoglycerides. The products thus liberated by this action are used by the adjacent cells as an energy source or stored for future use. The remaining cholesterol in these particles form HDL which in turn circulates in the bloodstream and is captured by **receptors** in the liver. Here, the HDL is packaged into VLDL which is further catalysed into LDL by lipoprotein lipase enzyme. It appears that it is these LDLs that are the key element in the development of atheroma and CHD.

Experiments conducted in rats demonstrate significant changes in LDL binding sites on the liver membrane when fed on a cholesterol-rich diet. Furthermore, a comparative study of carbohydrate-induced and protein-induced changes reveal the influence of high carbohydrate, high fat diet on LDL receptors (Rawat & Srivastava, 1988). Another study into the effects of cholesterol-enriched diets on genetically hypercholesterolaemic rats showed an overall decrease in **hepatic lipase** and **plasma lipoprotein lipase** activities (Sultan et al., 1988). This is further suggestive of dietary factors that form a crucial link in the onset and development of FH.

Numerous theories have been postulated with regard to abnormally high plasma [cholesterol]. Ordinarily, circulating LDLs are effectively removed by their attachment onto specific **surface receptors** of most cells. Once delivered inside the cells, it can be usefully metabolised (eg. cell membrane synthesis or energy production). However, in cases of excess dietary fat intake, in particular, saturated fats or deficiencies in the LDL receptors themselves, the plasma [LDL] becomes raised and alternative mechanisms for 'mopping up' these extra LDLs come into play. One theory suggests that scavenger WBC convert these excess LDLs into '**foam cells**' which constitute a major component of atheromatous plaques (xref. Figure 3). Equally however, it should be noted that raised plasma [cholesterol] may be **secondary** to another underlying condition such as hypothyroidism or poorly controlled diabetes mellitus.

Genes and FH

It is important to note that the term Familial Hypercholesterolaemia is essentially used to describe a group of **primary** lipid disorders resulting from inherent abnormalities in lipid metabolism. If untreated carries a particularly ominous prognosis; a 50% probability of developing premature atherosclerosis and ischaemic heart disease before 50 years of age (Price & Wilson 1997).

Primary hyperlipidaemias such as FH (ie. where no underlying pathology exists) are often genetically inherited, usually autosomal dominants with heterozygotes often showing intermediate degrees of hyperlipidaemia and risk of associated disease (Rees & Williams, 1995). Genetic considerations give a

useful alternative method of classification (xref Table 1). With FH, xanthomata (lipid deposits) are seen especially around the eyes and in a thickened achilles tendon. **Homozygotes** of this condition (Hyperlipidaemia Type IIa) with impaired receptor-mediated clearance of LDL, present with **Ischaemic Heart Disease,** icluding **MI**, in their 20s and 30s with a high risk of premature death. An important diagnostic approach should include a positive family history for such premature cardiac death. A typical clinical syndrome of high plasma[cholesterol] includes xanthoma, xanthelasma and ischaemic heart disease. The absence of other observable signs and exhibiting symptoms should prompt an investigation of a detailed family history. The genetic basis for the LDL-cholesterol receptor has been well researched with current awareness of over 300 different gene defects leading to FH (Uren & Rutherford, 2000).

Moreover, the endogenous process of cholesterol synthesis is inhibited by receptor-mediated endocytosis (ie. LDLs are taken up via specific receptors). When cells die and their constituents are degraded, then the cholesterol is returned to the plasma, adsorbed onto HDLs where they are esterified with long-chain fatty acids in the presence of the liver-derived enzyme **lecithin acyl cholesterol transferase** or **LCAT**. The resultant cholesteryl esters are subsequently transferred to VLDL ar LDL by a transfer protein in the plasma. This further contributes to plasma [LDL] and exacerbates risk in susceptible individuals.

HDLs are synthesised in the liver as disc-shaped particles of a **ApoA1** and **phospholipid**. They can acquire other apoproteins and play a fundamental role in lipid metabolism in that they attract excess free cholesterol from the tissues and other lipoproteins. The HDL enlarges as a result of acquiring cholesterol esters, a process increased by transfer of surface constituents from chylomicrons and VLDL. HDL is taken up by the liver where the cholesterol enters the cholesterol pool. Cholesterol cannot be degraded by any type of body tissue and its removal is via secretion from the hepatocytes into the bile unchanged or as bile salts. These HDL-associated events are known as the **Reverse Cholesterol Transport Pathway**.

LDL Receptor Abnormalities

One of the more recent theories of FH causes relates to the several distinct defects in the cell surface receptor (which is responsible for the uptake of LDL by peripheral tissue cells). The LDL recognises the ApoE protein with the highest affinity. Plasma levels rise in heterozygotes with the rarer homozygotes displaying an increase that is of a far greater extent. Several classes of mutations in the receptors have been recorded (Adapted from Whetton, 1997).

TABLE 3: – Lipoprotein receptor mutations that have been attributed to raised plasma [cholesterol] in FH *(Adapted from Whetton, 1997)*

Mutation Type	Characteristics
1	No receptor is synthesised
2	Receptors are synthesised but they do not reach the plasma membrane because they lack the signals for intracellular transport or do not fold properly
3	Receptors reach the cell surface but they fail to bind LDL normally because of a defect in the LDL-binding domain
4	Receptors reach the cell surface and bind LDL but they fail to

	cluster in the clathrin coated pits which are responsible for receptor internalisation via receptor-mediated endocytosis (due to a defect in the C-Terminal)

Individuals with FH, though do not feel that they have raised plasma [cholesterol] may exhibit symptoms of cardiovascular disease, which develops as a result of narrowing of the arteries. The symptoms can include a pressing, crushing, retrosternal pain possibly radiating to the arm or to the neck, associated with physical exertion or cold (angina pectoris). If the symptoms become more severe and sustained, it may be a sign of acute coronary thrombosis (heart attack/ MI) (Uren & Rutherford, 2000 and Haslett, 1999).

Though a genetic predisposition to FH has been highlighted, it is vital to mention other risk factors that place this condition in context with other CVS diseases. Table 3 below highlights some of the main factors that contribute to an increased risk of CHD (Adapted from Whetton, 1997).

TABLE 4: – Contributory factors that increase levels of CHD risk in individuals *(Adapted from Whetton, 1997)*

Risk Factor	Comment
Smoking	• Direct damage to blood vessels • Increased risk of blood clotting
Diet	• A diet made up of bread, fruits, vegetables & small amounts of lean meat, fish & olive oil is recommended. • A diet rich in antioxidant vitamins eg. E, C, β-carotene also potentiates the oxidation of LDL cholesterol
Exercise	Routines that regularly 'exert' the CVS are recommended as they increase the blood's ability to break up blood clots
Alcohol	Moderate consumption decrease the negative effects of the LDL cholesterol and increase HDL cholesterol. Too much however, raises BP, damages liver, having an overall adverse effect
Blood Pressure	Higher the BP, the greater the risk
Proportion of LDL : HDL Cholesterol	Higher the ratio, the greater the risk
Body Weight	Avoiding obesity prevents a raised BP and the development of diabetes.

Homocysteine and FH

Recent evidence for the role of the amino acid **homocysteine** as a risk factor for atherosclerosis is rapidly accumulating (Fallest-Strobl et al., 1997). A high plasma [homocysteine] induces pathological changes in the arterial wall and is therefore strongly associated with an increased risk of atherosclerosis, manifested as cardiovascular, cerebrovascular and peripheral vascular events. Susceptible individuals with FH are also assessed for hyperhomocysteinaemia, in particualr those with a strong family history of atherosclerosis.

With a lack of empirical data from scientific research that proves an irrefutable link between high homocysteine levels and occlusive vascular disease, the former largely remains a risk factor as opposed to a causal one. Fortunately, the treatment strategy is non-toxic and lowering plasma [homocysteine] can be adequately achieved through proper diet and vitamin supplementation especially Folic Acid (Burchett, 1999).

Moreover, the genetic predisposition is an important factor as this can modify the speed at which lifestyle factors operate. Molecular genetics has provided the final evidence of a link between environmental factors and genetic predisposition to atherosclerosis. Firstly, over-expression of certain human genes can protect mice against even the slightest increase in blood cholesterol that follows massive cholesterol feeding (Sultan et al., 1988). One such gene is that for the LDL receptor. The highest affinity ligand for the LDL receptor is **ApoE.** Transgenic mice that over express ApoE also resist elevation of blood cholesterol levels by dietary cholesterol. Thus, either the amount of **receptor** or the amount of **ligand** can be rate-limiting for clearing cholesterol from the blood. Secondly, targeted gene disruption of the ApoE gene leads to mice with very high blood cholesterol levels owing to impaired receptor-mediated clearance of remnant lipoproteins that normally depend on ApoE. Mild atherosclerosis is observed in mice, even on a fat-free diet (Whetton, 1997). These finding are no surprise; humans with defective ApoE or LDL receptor genes have been known for years – they develop atherosclerosis. It is the direct nature of the evidence that links **cause** and **effect** that is important.

So what is considered **normal range** for fasting blood [cholesterol] ? The following sets the current parameters that provide indicators for treatment. Guidelines vary slightly according to source and should be viewed in the context of risk rather than a definitive statement of ill health.

Category 1	Ideal Level	Less than 5mmol/L (200mg/dL)
Category 2	Mildly Elevated	Between 5 – 6.4mmol/L (200 – 246mg/dL)
Category 3	Moderately Elevated	Between 6.5 – 7.8mmol/L (250 – 300mg/dL)
Category 4	Very High (Severe)	Above 7.8mmol/L (> 300mg/dL)

(Ref: Uren & Collins, 2000)

The Role of Exercise in FH

Basic knowledge of health studies would reinforce the importance of good diet and moderate exercise in generating and maintaining well-being as well as ensuring the optimal functional capacity of the heart, lungs and circulatory system. Indeed, this has some basis; with reference to FH, studies on exercise levels indicate that regular physical activity has a favourable impact on common risk factors for atherosclerotic diseases (Bouchard, 1997). This would include lipid and lipoprotein metabolism; regular exercise has been shown to increase HDL cholesterol, lower LDL & total cholesterol, and increase **lipoprotein lipase** activity; the key enzyme in the conversion of VLDL to HDL. However, considerable work is required in order to determine who can benefit the most from aerobic exercise in terms of lipoprotein profile and what the optimal training programme should be for males and females across various age groups and among ethnic groups. Particular emphasis on specific clinical sub-populations who have high risk lipoprotein profiles and who are at risk from CHD may reveal a clearer understanding of levels of risk, prevention and onset of disease (Leon, 1997).

In the light of recent clinical trials, strong emphasis is now placed on **lipid lowering** as part of secondary prevention. This is a valuable advance. However, it may have led to the danger of underestimating the case for primary prevention ie. lifestyle modifications (xref. Table 4 – risk factors) in persons at high risk. This would strongly oppose the holistic approach to management of ill health and where drug treatment of conditions that can be prevented through appropriate lifestyle choices is considered a radical yet avoidable consequence of poor medical management.

In FH, this may not prove to be so clear cut, where dietary modification, or regular physical activity has minimal effect on total plasma [cholesterol] especially in severe cases where levels exceed 7.8mmol/L. Though orthodox medicine differs somewhat to Herbal medicine in its approach to diagnosis and treatment, in cases of FH, as will be illustrated shortly, the two practices share a common philosophy founded on the same physiological basis; namely, the cholesterol biosynthetic pathway as their targets for action.

Primary prevention strategies include significant dietary modification even in mildly elevated plasma [cholesterol]. Global concerns over the increasing prevalence of hypercholesterolaemia has not escaped marketing opportunities; the range of food products containing **plant stanol ester** (eg. Benecol™ and Flora ProActive™) is an example of how food manufacturers are meeting the demand for products to reflect the health-conscious consumer. Whether this is exploitative remains to be seen – though there is credible scientific data that supports the lipid-lowering effects of plant stanol ester (they decrease LDL levels by up to 14%; manufacturer's claim!!

For the purposes of this assignment, discussion will be restricted to the pharmacological action of **statins**; a class of drug which falls into the category of **HMG CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors.** In comparison, discussion will include the pharmacological action of **garlic**; one of the most widely-used culinary herb of increasing importance and recognition in medical practice.

Pharmacological Action of Statins

The clinical benefits of lowering cholesterol in both primary and secondary prevention of CHD are well established. Dietary and lifestyle modifications are key components in the treatment of hyperlipidaemia, though they may not achieve treatment goals. The majority of patients will require pharmacological intervention. The HMG CoA reductase inhibitors (statins) are the most effective and best tolerated lipid-lowering agents available (Laurence et al., 1997). Large scale intervention trials have established that the use of statins significantly decrease coronary events and death. Despite this evidence however, undertreatment of hypercholesterolaemia is common; many patients who may benefit are not prescribed a statin. The underuse of statins by those who would benefit the most has urged manufacturers of this drug to put forward proposals to the US FDA (Food & Drug Administration) to approve the over-the-counter availability of statins. Not surprisingly, this proposal has been recently rejected on the premise that it is the physicians who should probably determine who should get the drug as well as regulating the monitoring of side effects (Hulley et al., 2000).

This issue has been compounded by the fact that there is widespread variation in the prescribing of statins by medical practitioners. Perhaps the overriding issue of **cost** is more the concern as is the case with other drugs in urgent cases such as **Interferon** (an anti-viral cytokine used in the treatment for MS for eg.) and **AZT** (a reverse transcriptor inhibitor used to delay the onset of AIDS-associated symptoms) rather than limited clinical monitoring and the mismanagement of OTC availability !

HMG CoA reductase inhibitors are becoming a mainstay in the management of patients with established CHD (secondary prevention) and they hold great promise for treatment of high risk patient s without evident CHD (primary prevention).

There are currently 5 statins available on the market, namely: ***simvastatin, pravastatin, fluvastatin, atorvastatin*** and ***cerivastatin***; all of which share the same mode of action. They competitively inhibit the HMG CoA reductase; the rate-limiting enzyme in cholesterol synthesis. The resultant fall in hepatocellular cholesterol causes an up-regulation of hepatic LDL receptors which bind circulating LDL cholesterol. The increased uptake of LDL cholesterol results in a reduction in plasma cholesterol accompanied by a slight increase in HDL cholesterol and triglycerides (National Medicine Information Centre, 1999).

Statins achieve on average a 25 – 30% reduction in cholesterol. In addition to their lipid-lowering properties, angiographic studies (ie. a study of angiograms) have shown that statins slow the rate of progression of atherosclerosis, promote plaque regression and stabilise atherosclerotic plaques prone to rupture. Suggested stabilisation mechanisms include antithrombotic, anti-inflammatory and antioxidant mechanisms, together with restoration of endothelial function. The most appropriate route of administration of statin appears to be in tablet form ie. oral preparation. Approximate dosages for each type of statin is given in Table 5; BNF, 2000).

TABLE 5: – Dosages of standard preparations of the statins in the orthodox management of FH *(Taken from BNF,2000)*

- ***Atorvastatin*** 10 – 80mg/day
- ***Cerivastatin*** 0.1 – 0.3mg/day
- ***Fluvastatin*** 20 – 80mg nightly
- ***Lovastatin*** 10 – 80mg nightly with evening meal or in divided doses
- ***Pravastatin*** 5 – 40mg nightly
- ***Simvastatin*** 5 – 40mg nightly

Brief pharmacodynamics indicate that the dose-response curve for statins is such that the dose determines the % reduction **not** the **absolute** reduction in LDL cholesterol. It follows that a larger dose or a more potent statin is required to lower LDL cholesterol by a given amount eg. 40mg/dL or 1mmol/L. Moreover, notable pharmacodynamic considerations include important drug interactions, in particular the increased risk of myopathy and of potentially fatal rhabdomyolysis when certain statins are combined in administration with cyclosporin, tacrolimus, nicotinic acid, fibrates, erythromycin, azol antifungal agents and some Ca^{2+} channel blockers including *Mibefradil*.
There are profound differences between the metabolism of statins and hence major differences in their potential for drug interactions (http://www.chd.taskforce, 2000). Grapefruit juice has been shown to interefere with the metabolism of some statins whilst renal failure is a risk factor for muscle side effects in others. Reported side effects of statins include headache, flatulence, constipation, dyspepsia and elevation of transaminases; rare side effects also include pruritis, rashes and

erythematosus though the effects are usually reversible on withdrawal of the drug (Laurence et al., 1997).

Herbal Approaches to FH Treatment

In a climate of increasing disenchantment with orthodox medications, alternative therapies such as herbal remedies are proving to be a more suitable option for a range of common ailments as well as for a number of more serious disorders. This appears to be the case in point with regard to FH where herbal approaches considers the use of key herbs such as *Curcuma* (turmeric), *Commiphora mukul* (guggul) and *Cynara* (globe artichoke) (Mills & Bone, 2000). However, it is **garlic** and its various preparations that prove to be the herb of choice and supported by credible scientific data that illustrates its efficacy in lowering plasma [cholesterol], it may be prescribed by physicians more readily than statins.

Extensive research into its chemical constituents as well as its application in clinical medicine has revealed the enormous potential and scope for the uses of this popular herb. Comparisons of Mediterranean and traditional Indian diets, where garlic is a predominant ingredient highlights a link between the consumption of garlic in significant quantities to the low incidence of heart disease in those countries (Fulder, 1997). Again, experiments on animal models fed on a cholesterol-rich diet together with different kinds of dried garlic powder and extract showed that garlic reduced blood [cholesterol] by about a **quarter** and liver [cholesterol] by more than **half**. Larger amounts of garlic over a considerable period were shown to reverse the fat build up in arteries though the remit of orthodox medical research offers resistance to such findings and as such, this remains debatable.

Observations on human populations therefore warranted serious study into the efficacy of garlic and its components conferred to its cholesterol-reducing ability. Since 1975 there have been over 32 human studies demonstrating the lipid-lowering effects of garlic (Robbers & Tyler, 1999). The majority of these studies were randomised, double-blind, placebo-controlled, lasted 4 – 16 weeks and used hyperlipidaemic patients. Double-blind trials on cholesterol-reducing effects of garlic, conducted in humans show a clear correlation between garlic intake and plasma cholesterol reduction (Ernst, 1996). This has been graphically represented using data from a classic German study conducted by F. H Mader in 1991. So what key ingredients are present in garlic that confers its unique medicinal properties in relation to FH ?

Alliin is the ingredient in garlic which, when it is converted to **Allicin**, is believed to be most responsible for the lipid-modifying and anti-thrombotic effects (Miller & Murray, 1998). A brief pharmacological review suggests a mode of action at **two** sites in the metabolic pathways of cholesterol synthesis, namely in the early phase (**HMG CoA reductase**) and in the late phase (**14α-demethylase**). What is particularly noteworthy here however, is that in addition to other garlic studies, results show that the inhibition of endogenous cholesterol biosynthesis occurs as a physiological response to the ingestion of certain plant constituents (Schulz et al., 1998).

Although conflicting reports exist on the most effective preparation for garlic administration, most are in agreement on its oral form, whether fresh, dried, powder or standardised extracts. Owing to variations in commercial preparations, one would be excused in thinking that fresh preparations are more efficacious than other forms. Surprisingly, enteric-coated capsules or tablets of freeze-dried garlic appear to be more effective than fresh garlic owing to the fact that the active principles are released in the mouth during chewing, and not in the stomach as originally thought. This is because

the enzyme **alliinase,** naturally present in garlic in significant quantities, is destroyed by the stomach acid (Tyler, 1993). Of course one can overcome this problem by thorough chewing of fresh garlic, retaining it in the mouth for a longer period prior to swallowing, thereby increasing its effectiveness – this unfortunately proves rather a unpalatable and distasteful procedure to most, if not, at least anti-social!!

Phamacodynamics is such that consumption of moderate quantities of garlic, even on a daily basis should not pose any particular health risk for normal persons (Tyler 1994). Pharmacodynamic findings in FH cases are very limited and inconclusive at present. That stated, the larger amounts of garlic apparently required for therapeutic utility (>5 cloves/day) can result in heartburn, flatulence and related gastrointestinal problems. Moreover, some may even experience allergic reactions. Consumption of large quantities of garlic has been contra-indicated in those taking aspirin or other anticoagulant drugs due to garlic's associated anti-thrombotic properties (ie. it increases clotting times).

CONCLUSION

In summary, it can be seen that a clearer understanding of biochemical mechanisms and major pathways of lipid metabolism has enabled treatment strategies that can be more specifically targeted at the rate-limiting steps in cholesterol biosynthesis. This refined approach to orthodox management with the use of HMG CoA reductase inhibitors (statins), has led to the successful lowering of plasma [cholesterol] which exhibit characteristic, clinical features of FH.

However, equal emphasis on primary prevention strategies that include lifestyle modifications, such as a proper diet, would be very much in keeping with the holistic philosophy of herbal medicine practice. With this in mind, the use of garlic and the fact that it has widespread use and popular appeal in the culinary world, continues to provide a practical alternative that has a high patient compliance and minimal side effects compared to its orthodox counterpart.

From the pharmacological perspective, the fact that scientific research has revealed a valuable insight into its mode of action, means that garlic should be seriously viewed in a similar light to conventional medicines currently prescribed in the treatment of FH. If detailed knowledge of cellular mechanisms and mode of action for all herbal remedies were available, perhaps we may witness significant advances in treatment of some of the most invasive, infiltrative and chronic diseases that have continued to baffle the medical sciences for years.

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THE NUTRITIONAL ASSESSMENT OF A 36-YEAR OLD HYPERCHOLESTEROLAEMIC FEMALE BASED ON A 3-DAY DIETARY RECALL

ABSTRACT

The influence of dietary intervention in the control of mildly elevated familial hypercholesterolaemia is well established and documented. A dietary assessment of a subject in this risk group by computer programming, reveals acceptable levels of saturated fat intake, particularly cholesterol though proportionately, the total fat intake is above recommended values. Similarly, carbohydrate and protein intake also indicates consumption exceeding the recommended levels despite total energy intake being below acceptable values. Moreover, a number of important vitamin and mineral deficiencies shown by these findings have significant long-term implications in this subject. In this regard, dietary assessment provides valuable determinants in formulating appropriate nutritional advice for addressing obvious dietary deficiencies.

Although no one method for conducting dietary analysis can be entirely rigorous in respect of scientific protocol, detecting subtle nutritional imbalances can prevent medical consequences of long-term deficiencies through immediate/ short-term dietary intervention. Equally, the limitations of this assessment and discrepancies in methodology must be considered prior to making dietary recommendations as a basis of nutritional therapy.

INTRODUCTION

Definition & Association with CVD

Familial hypercholesterolaemia is an inherited disorder of lipid metabolism with various clinically defined categories. Genetic abnormalities give rise to breakdown of the usual mechanisms for food production, storage, transport or utilisation of cholesterol, triglycerides or lipoproteins. This has important implications in subjects who need to maintain serum [cholesterol] within acceptable limits.

The association between serum cholesterol elevation and an increased risk of premature and severe atherosclerosis is well established with numerous interactions between dietary fat, lipid metabolism and atheroma development (Heller et al., 1987). Current parameters that provide a rationale for treatment vary slightly according to source and should be viewed in context of risk rather than a definitive statement of ill health. The subject in this experiment has a total [cholesterol] of 6.2mmol/L (200-246mg/dL); this is categorised as being in the upper limits of mildly elevated, as indicated below:

Levels of Risk

Category 1	Ideal Level	Less than 5mmol/L (200mg/dL)
Category 2	Mildly Elevated	Between 5-6.4mmol/L (200-246mg/dL)
Category 3	Moderately Elevated	Between 6.5-7.8mmol/L (250-300mg/dL)
Category 4	Very High (severe)	Above 7.8mmol/L (>300mg/dL)

(From: Uren & Collins, 2000)

Important Functions of Cholesterol

Despite the adverse publicity surrounding dietary cholesterol consumption, this principle sterol has an important structural role in membranes and lipoproteins, in addition to being crucial as a precursor to bile acid formation, steroid hormone synthesis and vitamin D. Physiologically of course, it is also important in nerve (saltatory) conduction as a component of myelin sheath.

Dietary Implication in Hypercholesterolaemia

Genetic determinants of mildly elevated serum total [cholesterol] imply that drug intervention is the inevitable course in therapeutic management in this subject. This may have some validity, however, empirical data reveals that prevention strategies including significant dietary modification can be equally effective in controlling plasma [cholesterol] (Sultan et al., 1988). It has to be recognised that although dietary modification is a key component in the treatment of hypercholesterolaemia, it may not achieve treatment goals.

Good dietary and lifestyle practices are always advocated and with reference to the general population, there is easy access to a substantial amount of information on nutrition and its importance in optimum health. In respect of the subject in this experiment, dietary control and intervention is significant, particularly in the absence of drug management. Effective control of serum [cholesterol] must address issues of daily fat intake, nutritional status and preventative measures for CVD including aerobic/cardiovascular exercise.

Reasons for Dietary Assessment

Dietary assessment has a number of benefits which extends to all groups of the population, but more specifically to vulnerable groups and those with established health risks. Analysis of energy intakes may determine treatment rationales for those who are clinically underweight or equally, those who are chronically obese. However, it is the subtle imbalances between requirement and intake that may prove to be of maximum value in the clinical setting. Similarly, assessing nutritional status in subjects via dietary analysis may indicate previously undetected dietary/nutritional deficiencies that may have long-term consequences on health. This has added emphasis, particularly if such deficiencies (or indeed excess, in some cases) demonstrate proven contributory risk to current health concerns (for instance, excess saturated fat intake in mildly elevated hyperlipidaemia).

Moreover, in attempting to optimise health, dietary assessment may highlight good and bad practices with reference to diet and nutrition. This may reveal a direct link between poor nutritional practices and symptomology in diet-related disorders. Furthermore, adapting conventional practices in formulating special diets for specific health problems may be exclusively reliant on vital information that is ascertained only through a formal dietary analysis.

Aims & Objectives of this Experiment

The dietary assessment of the subject in this study has a number of important objectives:

- to examine energy intake by comparing recommended values as stated in the COMA report of 1991,
- to analyse nutritional status via comparisons of macronutrient and micronutrient intake with DRVs as recommended in the COMA report of 1991,
- to examine nutritional imbalances by assessing whether important aspects of dietary requirements are met,
- to examine and assess fat intake specific to requirement, ie. to quantify and qualify the type of fat especially in relation to hypercholesterolaemia (to assess whether they are within acceptable limits specific to the subject's requirement) and
- to suggest appropriate guidelines for dietary recommendations based on the findings of the dietary analysis.

MATERIALS & METHOD

Materials:

1. 1 subject
2. weighing scales (kg and g)
3. measuring jug (ml amd L)
4. computer software package for conducting dietary analysis
5. DRVs as published in the COMA report of 1991
6. previously recorded information on personal profile – height, weight, health status etc…

Method

A 3-day dietary recall was carried out on a 36-year old hypercholesterolaemic female. This experiment was conducted over 3 consecutive days with all foods being weighed in grams(g) and all drinks & beverages being measured in millilitres(ml), giving details of times and places when the foods were consumed. This information was recorded (xref. Dietary Intake Record Sheets; Appendix 1) over a 3 day period that included a weekend day (Sunday) and 2 weekdays (Monday & Tuesday) in order to account for potential differences in food consumption patterns in a typical week.

Only the foods consumed were recorded, not left overs from meals, peels or stones from fruits etc….Similarly, only foods in their cooked form were used for analysis, though provision was made for raw foods in the software package. All discussion of data were based on this analysis with comparisons being made to DRVs as published in the COMA report of 1991.

Recorded weights and measures of all foods consumed in this 3 day period were input into the computer package (as specified) and a dietary analysis was instructed on this subject.

RESULTS

Dietary analysis carried out using the dietsure.com software package reports a number of findings. The subject in this study has a daily energy intake of 1355kcal which compares to 73.5% of the recommended value for a female in this age group (xref. Tables 1-3). Of this, 51.6% is provided from carbohydrates (22.2% starch and 29.4% sugars), 17.7% from protein, 29.2% from fat (14.3% monounsaturates, 6.8% polyunsaturates, 8.1% saturates) and 1.5% from other sources. This has been illustrated in Fig. 1. Comparisons with DRVs for macronutrient content reveals that all nutrients are in excess of the recommended intakes (xref Table 4 and Fig.4).

Subject Profile:	Age :	36 years 6 months
	Gender Group :	Female
	Height :	1.53m
	Weight :	47kg
	BMI :	20.1
	Occupation :	Light
	Lifestyle :	Moderate
	Days in diet :	3

Table 1 : Sources of energy as a proportionate value of the daily total (1355kcal)

Source of Energy	% Contribution of the daily total
Carbohydrates	51.6
Protein	17.7
Fat	29.2
Other	1.5

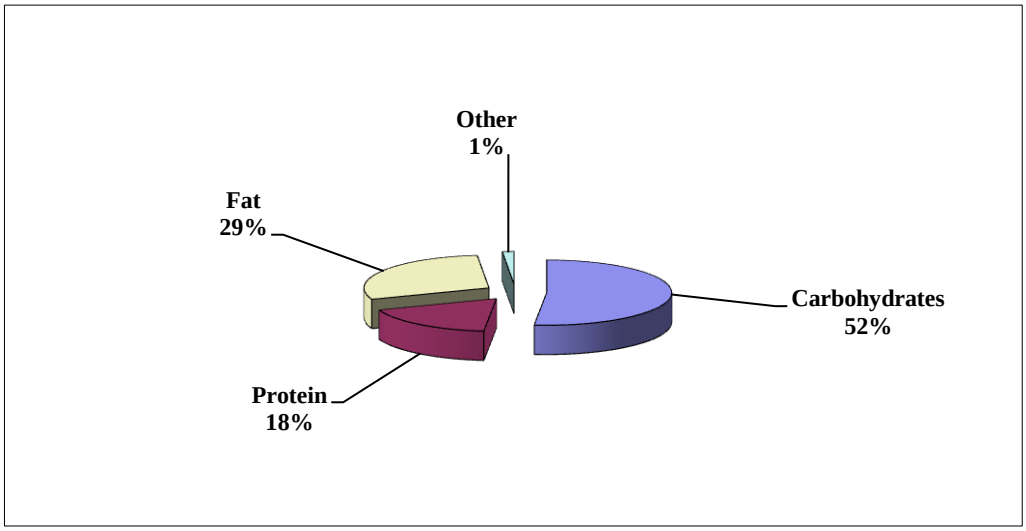

Fig 1 : % Energy from food sources based on average daily intake

Table 2: % Energy from carbohydrate sources

Type of Carbohydrate	% Contribution to daily energy intake
Starch	22.2
Sugars	29.4
Other	0.4

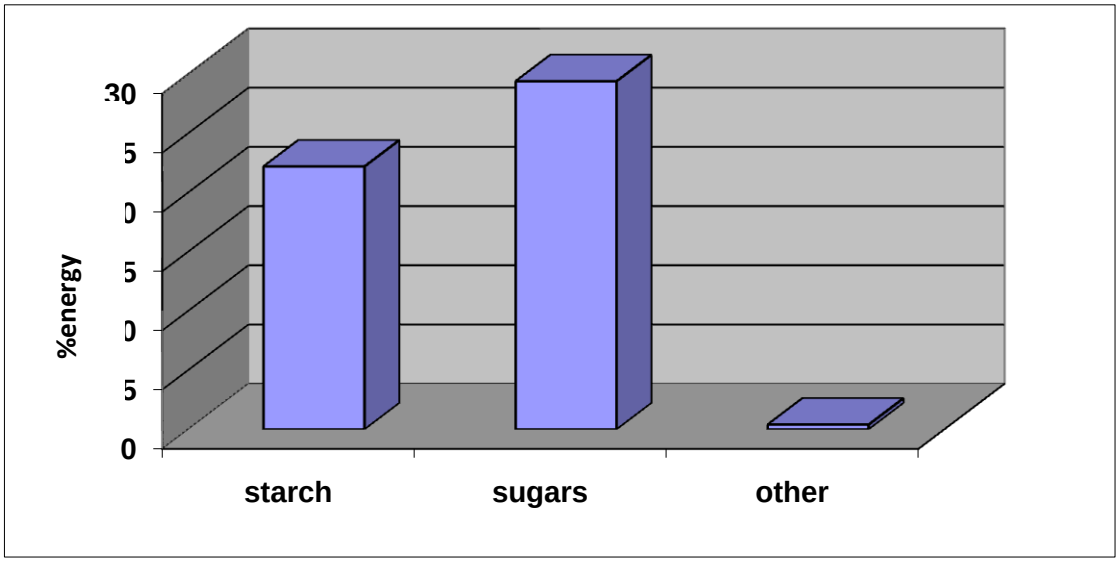

Fig.2 : % Energy from carbohydrate sources

Table 3: % Energy from fat

Type of Fat	% Contribution to daily energy intake
Monounsaturated	14.3
Polyunsaturated (PUFA)	6.8
Saturated (SFA)	8.1
Other	22.1

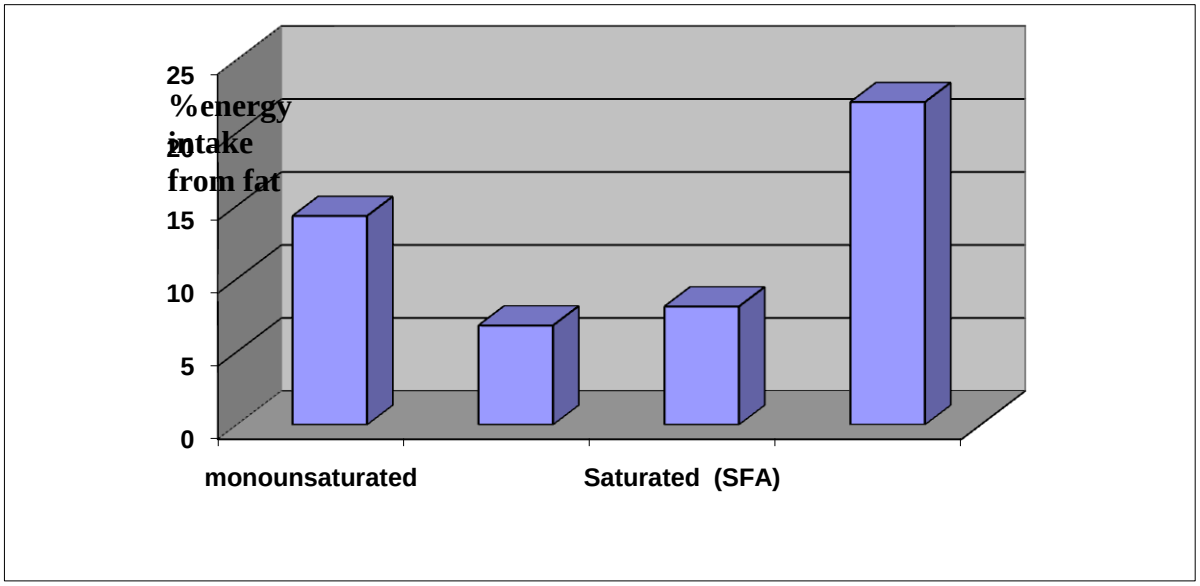

Fig. 3 : %Energy from fat

Table 4 : Average daily macronutrient intake

Nutrient	Daily Intake (g)	%RNI (UK)
Carbohydrates	188.0	110.0
Protein	60.0	133.0
Fat	77.0	155.4
Fibre	16.5	68.9

NB. Fibre is classed her as a nutrient for comparison purposes though it has no nutritional value , it is essential for optimum digestive function

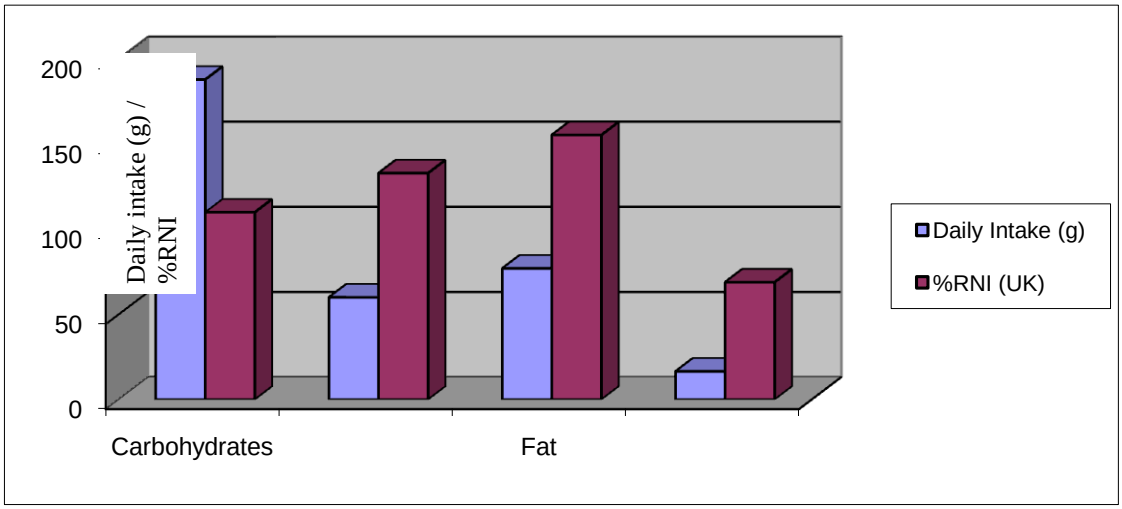

Fig 4: Comparisons of %RNI (UK ref values) of macronutrients based on average daily intake

Of particular relevance in this subject is the total fat intake (xref. Table 5) especially the saturated fat intake. The findings of the report states that the saturated fat (SFA) and cholesterol intake is sensible and not in excess (81.1% of RNI). Moreover, the polyunsaturated fat (PUFA) content adequately meets RNI(113.6%. However, the total fat content in this subject far exceeds recommended values at 155.4% of RNI (xref. Fig 5). The report also finds that the proportion of energy derived from fat in the diet is in fact too high (Fig. 3) and makes suggestions for substituting low fat alternatives.

Table 5 : Average daily fat intake

Fat	Daily Intake (g)	%RNI (UK)
Total	77.0	155.4
PUFAs	10.3	113.6
SFAs	12.2	81.1

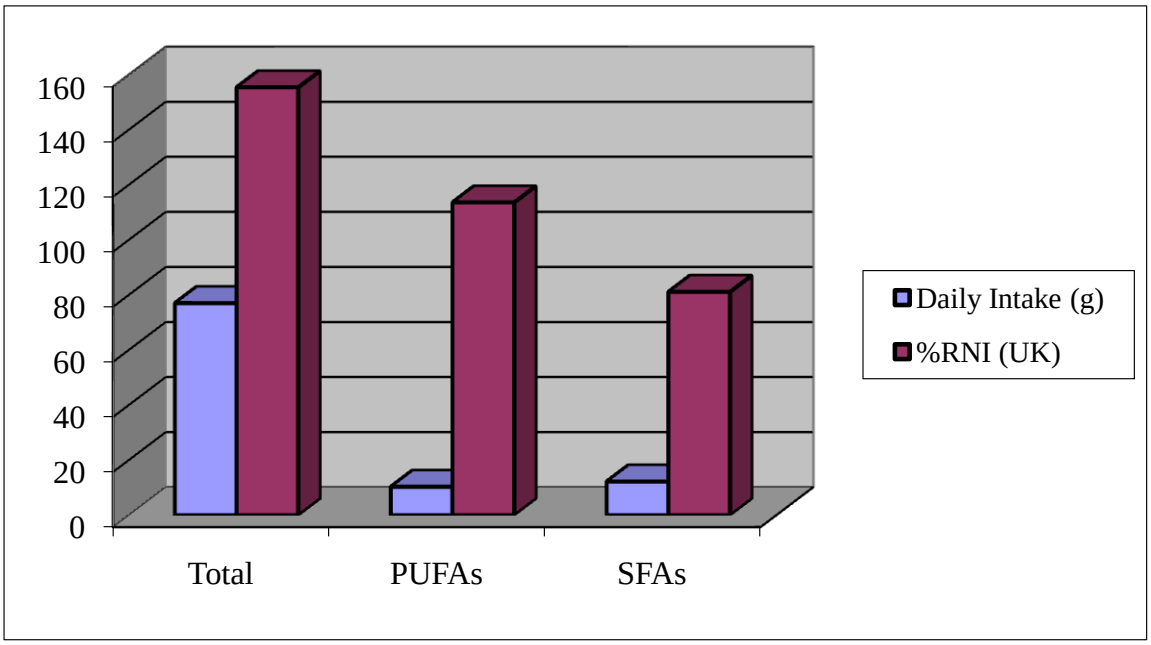

Fig 5 : Comparisons of %RNI (UK ref values) of fat consumption based on average daily intake

Table 6 : Average daily micronutrient intake

Micronutrient	Daily Intake (mg/µg)	%RNI (UK)
K^+	2606mg	74.5
Ca^{2+}	495mg	70.7
Mg	280mg	103.9
P	949mg	172.6
Fe^{2+}	6.9mg	46.5
Cu^{2+}	1mg	97.0
Zn^{2+}	5.6mg	80.5
Cl^-	1908mg	76.3
Na^+	1451mg	90.7
Se	24.6µg	41.0
I	54.4µg	38.9
Vit B_1 (Thiamin)	1mg	184.7

Vit B_2 (Riboflavin)	1mg	93.0
Vit B_6	1.5mg	164.7
Vit B_{12} (Cobalamine)	0.2µg	13.3
Nicotinic Acid (Niacin)	30mg	336.3
Folate	186µg	93.0
Vit A	1356µg	226.0
Vit C	171mg	428.4
Vit E	8.3mg	201.3

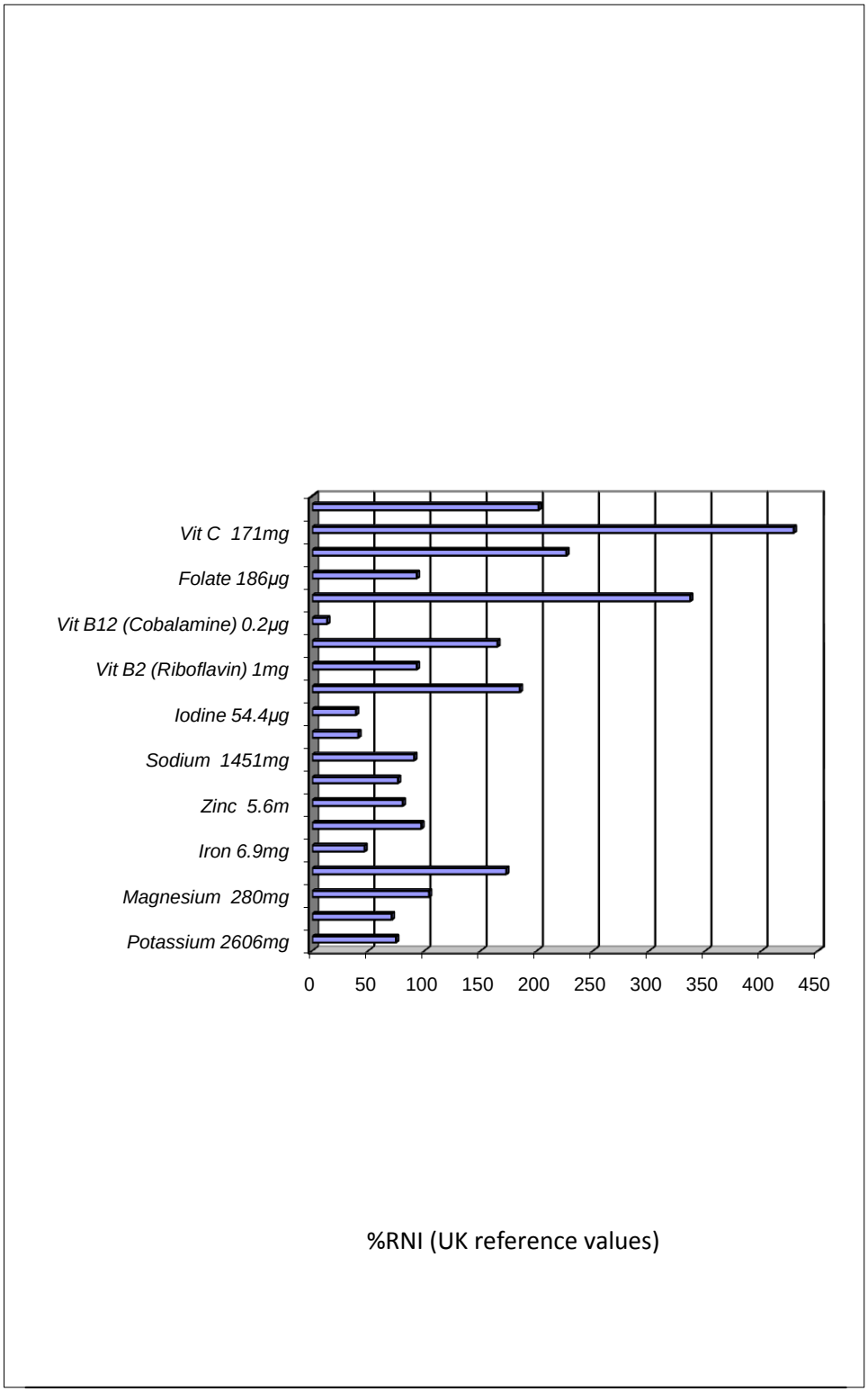

Fig 6 : Comparisons of %RNI (UK ref values) of micronutrients based on average daily intake

The fibre (NSP) content is below the recommended intake by only meeting 68.9% of the RNI.

The average daily micronutrient intake has been detailed in Table 6 and graphically represented in Fig. 6. The report finds that the subject is deficient in a number of important vitamins (Vit B_{12} and folate) and minerals (Ca^{2+}, K^{+}, Fe^{2+}, Zn^{2+}, Cu^{2+}, Se, I). Conversely, the following micronutrients are reported to be consumed in excess: P, B_1, B_6, Vit A, Vit C, Vit E, Niacin (xref. Table 6). No analysis of water intake was carried out.

DISCUSSION

Assessing Nutritional Status

The results of the dietary analysis in this subject has revealed a number of important findings. Though energy intake meets only 73.5% of the recommended daily value, all 3 macronutrients are in excess of the desired intake. Much of this is contributed by fat (155% of RNI) which provides more than double the energy value of protein or carbohydrate (at 17KJ/g of nutrient compared to 38KJ/g for fat). The fat intake is significant here owing to the moderately elevated, circulating cholesterol in this subject. Though in excess of the recommended total fat intake, cholesterol and SFA content of the subject's diet is within acceptable limits. The subject makes a conscious effort in reducing SFA and increasing PUFA intake. The consumption of 'good fats' may contribute to the total fat intake which reads high as a result. The report gives no indication of the discernable difference in the types of fat consumed and makes suggestions for low fat alternatives. This is highly misleading. Interestingly, a recent publication into high fat diets and CVD susceptibility suggests that in high-risk groups, a greater emphasis should be placed on sugar consumption rather than fat (Vines, 2002).

Similarly, protein intake is also reported as moderately above recommended values. This subject has a predominantly vegetarian diet with the occasional poultry or fish meal. The analysis does not account for the type of protein (ie. 1st or 2nd class) nor the source (ie. whether animal or vegetable). The premise that all proteins be classed in one sole category is scientifically and nutritionally inaccurate. The assessment of nutritional status based on this is therefore limited and more quantitative, which can be misleading to participants. However, it does provide a broad indicator of protein intake and can be clinically useful. This is made more pertinent particularly in light of evidence suggesting that excessive consumption of proteins (either animal or vegetable sources) may contribute to a variety of health risks including obesity and associated illnesses (protein-rich foods are often high fat foods) and some studies suggest a link between high meat diets and colon cancer (Kushi et al., 1995). It may also contribute to bone demineralisation due to Ca^{2+} depletion; protein excess promotes Ca^{2+} excretion via the kidneys leading to a steady loss from connective tissue (bone).

Moreover, the fibre intake is low; this may further predispose the subject to CVD (low fibre intake is linked to increased risk of heart disease).

Analysis of micronutrient intake content reveals some alarming findings, particularly in the number of mineral deficiencies (xref. Table 6; Results). This has many implications in respect of long-term health risks and must be viewed in context with current health status of the subject. Interestingly, there are also a number of micronutrients which are consumed in excess (xref. Table 6; Results). Though much of the medical emphasis is placed on insufficient intake, there is limited, incontrovertible empirical data of clinical significance on the deleterious effects of micronutrient excess. Issues of toxicity and contribution to major diet-related disorders remain speculative at present (Zeisel, 2000) and

discussion is focused on promoting good nutritional practices rather than advocating the indiscriminate administration of supplementation. In this subject however, such imbalances in micronutrient intake remains a cause for concern according to the dietary analysis.

In respect of Ca^{2+}, the subject has eliminated most dairy produce from the diet due to their high fat content and takes supplements to meet daily requirements. There is the possibility of iron-deficiency and pernicious (Vit B_{12} deficiency) anaemias. Risk is increased with insufficient intake of folate which falls below recommended amounts.

Advantages & Disadvantages of Method

Though no one assessment can be comprehensive for all groups of any given population, there are a number of benefits in conducting dietary recall analysis in attempting to address nutritional status; this has been highlighted in the Introduction. A critique of this assessment method however, reveals a number of discrepancies which not only demonstrates a lack of scientific rigour in the methodology but also calls into question the entire procedure in any dietary assessment itself as well as its clinical utility. In the first instance, the subject in this experiment will probably fall within the 5% bracket of the population chosen to establish DRVs. Ideally, comparisons of nutrient intake should have been compared with DRVs in similar subjects with hypercholesterolaemia and with similar dietary habits. Therefore, how relevant or appropriate is the use of DRVs of the COMA report (1991) in this subject?

There are also contradictory statements in the report which is confusing to those who want accurate information that can form a basis for guidelines in improving nutritional practices. For eg. linoleic acid intake has been assessed as extremely high (2629.3% of RNI !); there is no mention of whether this is beneficial to the subject or not. Interestingly however, though there is no empirical evidence of adverse effects of excess consumption, the COMA Report (1991) suggest recommended values for linoleic acid at 1% of the total energy intake and linolenic acid at 0.2% of the total energy intake. Moreover, considerations of rate and extent of nutrient absorption at the cellular level in addition to factors affecting metabolic mechanisms in digestion, absorption and assimilation appear to be redundant in this analysis. Pharmacokinetic and pharmacodynamic effects in any subjects on medication is not considered either; substantial evidential data demonstrates the effect of food-drug interaction (Pinto, 1991). This has important consequences for absorption of essential nutrients. These are major limitations in this assessment method.

There are also unaccountable losses and gains in essential nutrient status in this subject eg. leaching of Fe^{2+} via large tea consumption, food combination may inhibit absorption through biochemical interaction or competition at the cellular level, consumption of fortified foods will add to micronutrient content, extraneous introduction of micronutrients through use of skincare products with added vitamins (especially A, C and E); parenteral absorption via the skin. Equally, the presence of additives or preservatives in the pre-packed foods consumed have not been accounted for either.

The timing of consumption is of crucial importance in assessing nutritional status. It is well-established that the natural biorhythms and diurnal activities of digestive enzyme secretion and regulatory hormones that influence intestinal function, have a profound effect on the entire digestive process. Dietary analysis does not take this into account. Additionally, there is no consideration of preparation, cooking and processing methods that have a significant bearing on actual nutrient intake. Furthermore, the software package used in this experiment does not provide a fully comprehensive list of foods ; consequently, the closest-resembling item of equal weight/volume was chosen. Neither is there provision for vitamin/mineral supplementation. There are further discrepancies in inputting raw vs cooked foods; a significant and crucial detail. This does not

constitute good scientific protocol and the subsequent dietary analysis is in fact rather inaccurate and open to misinterpretation.

Sources of Experimental Error

1. Discrepancies in methodology	input of data eg. Itemised inclusion of milk in tea/coffee
2. Query duration of experiment	are 3 days sufficient ? Difficulties encountered in fitting the experiment into daily routines and activities
3. Limited considerations	eg. lifestyle, food combination, timing of food consumption, metabolic rate (basal) etc…
4. Recording protocol	not entirely accurate or specific for some foods eg. Raw vs cooked, pre-packed foods etc….closest-resembling items chosen; lacks scientific rigour
5. Query comparison using DRVs for a standard population	
6. Issues of compliance	poor on occasion, some foods omitted from record

Dietary recommendations based on findings

- increase intake of deficient micronutrients
- increase intake of Ca^{2+} and Vit D to address bone health (can choose alternative low fat dairy produce eg. cottage cheese or even non-dairy foods)
- reduce protein intake; excess can be harmful
- continue to observe total fat intake particularly saturated fat and cholesterol
- increase NSP (fibre) intake; currently only meets 68.9% of RNI
- increase energy intake via sources other than fat; only meets 73.5% of RNI.

SUMMARY

This dietary assessment has revealed a number of general findings regarding the nutritional status of this subject. Recommendations were made based on the information provided in the dietary analysis report which gives useful advice on intakes of total energy, macronutrients, micronutrients and NSP (fibre). The important health implications for this subject in respect of saturated fat intake, particularly cholesterol suggest a greater emphasis on sugar in case of mildly elevated hypercholesterolaemia.

Though no one method of dietary assessment can address all the issues and limitations as discussed, the clinical utility, accuracy of the procedure and practicality of implementation are all important considerations which must be accounted for.

In setting a protocol for assessing nutritional status, all such considerations must be adequately addressed in order to ensure scientific rigour, particularly if assessment is entirely dependent solely on this method. In the context of good nutritional practice and the maintenance of optimum health, it is always best to adhere to the time-honoured advice of balance, moderation and knowledge of one's own system, especially in relation to the increased incidence of food sensitivities, intolerances and allergies (Brostoff & Challacombe, 2002). Though this subject may fall within a small percentage of the overall population, this dietary assessment method provides a broad, general indication of obvious imbalances in nutrient intake with overriding health concerns. Considering the fact that diet and ill health are inextricably linked, an initial assessment, however crude with reference to accepted scientific application, can avert long-term consequences associated with poor nutritional practices.

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