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# 2

# Homocysteine is Elevated in COPD

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## 1. Introduction

Homocysteine was first described by Butz and du Vigneaud in 1932 (Butz 1932). An association between elevated homocysteine levels and human disease was first suggested in 1962 by Carson and Neil (Carson 1962). They had found high homocysteine concentrations in the urine of some children with mental retardation.

In 2000, Yi and Melnyk found that plasma total homocysteine is positively associated with parallel increases in plasma S-adenosylhomocysteine and concentrations and lymphocyte DNA hypomethylation. This lead Medina and Urdiales (2001) to speculate on an indirect mechanism for homocysteine pathogenicity secondary to inhibition of DNA methytransferase and that is the disruption of DNA methylation patterns leading to alterations in gene expression which may be of significance in chronic diseases many of which are associated with elevation in homocysteine. Elevated plasma homocysteine has been associated with neural tube defects, cognitive impairment in the elderly, psoriasis and some tumours (Refsum 1998). Hyperhomocysteinaemia has also been associated with cardiovascular disease, atherosclerosis, venous thrombosis, diabetes mellitus and renal failure (Okuyan et al, 2010; Refsum et al, 1998; Givvimani et al, 2011; Kim et al, 2011; Hankey & Eikelboom, 1999; Dominguez et al, 2010; Wile et al, 2010; Austen et al, 2003). Plasma HCY has also been related to clinical outcome in acute respiratory diseases (Tsangaris et al, 2009). This widespread involvement of homocysteine in disease explains the current interest of both basic and clinical biomedical scientists in this amino acid and thus the explosion of articles containing homocysteine as keyword.

There has hitherto not been much interest in homocysteine disorders in respiratory disease. Sanguinetti was one of the first researchers to postulate that there was an imbalance between redox reactions in COPD (Sanguinetti 1993). In an elegant series of experiments, Rahman et al showed that reduced glutathione was depleted by exposure to cigarette smoke in alveolar epithelial cells (Rahman et al 1995). Further work by this group revealed that there is loss of antioxidant capacity in COPD relative to healthy non-smokers (Rahman et al

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2000). These results were supported by Andersson who showed that high plasma homocysteine levels were associated with low reduced glutathione levels in 2000 in the plasma of COPD patients (Andersson 2000). Thus establishing an almost inverse relation between the levels of homocysteine and reduced glutathione and giving rise to the hypothesis that homocysteine should be elevated in COPD because of impaired oxidative stress. Taken together this series of studies demonstrate that COPD, the most common chronic respiratory disorder, is linked to hyperhomocysteinaemia.

Chronic obstructive pulmonary disease is a disease mainly of the middle-aged and elderly. It results from an abnormal pro-inflammatory response of the lung to inhaled noxious stimuli that leads to an unrelenting accelerated decline in forced expiratory volume in the first second of exhalation (FEV1) and is characterised by a ratio of FEV1 to forced vital capacity (FVC) of less than 70%. The disease is currently estimated as the fourth leading cause of death world-wide and it is expected to become the third leading cause within the next ten years (GOLD 2010).

In this chapter we will examine the evidence for the association of hyperhomocysteinaemia and COPD and discuss its implications.

## 2. Homocysteine metabolism

Homocysteine is a 4-carbon amino acid attached to a sulphydryl group. Homocysteine is involved in the transfer of methyl groups when it is synthesized from S-adenosylmethionine methylase and adenosyl-homocysteinase (please see Figure 1). Homocysteine may also be transformed back to methionine or catabolised to cystathionine. In the latter pathway, homocysteine combines with serine via cystathione beta-synthase to yield cystathionine which, via a gamma-lyase enzyme, is cleaved to yield free cysteine and a ketobutyrate. Cysteine is then metabolized via gamma-glutamyl synthase/glutathione synthase to reduced glutathione (GSH) which is important for electron storage with oxidized glutathione (GSSG), as shown in Figure 1. Homocysteine is therefore linked to two important pathways in the body one involving methylation processes and the other a transsulphuration pathway that may be of importance in redox reactions in the maintenance of homeostasis (Medina et al, 2001; Giusti et al, 2008). Figure 1 shows how closely intertwined these two pathways are.

A further role for homocysteine may arise out of its capacity to bind to transfer ribonucleic acid (tRNA) which in certain circumstances is thought to produce a highly reactive derivative, homocysteine thiolactone (Jakubowski & Goldman, 1993; Jakubowski 2000). Homocysteine is usually immediately methylated to methionine-tRNA but when this process is impaired or inadequate, the reactive species, homocysteine thiolactone, is formed (Antonia et al 1997). This form of HCY can rapidly homcysteinylate any of several enzymes causing alteration in enzyme activity thus leading to disordered homeostasis and redox imbalance (Booth et al, 1997).

In spite of the above rather interesting theory it was not known how plasma HCY enters cells to affect such change. The transporter for HCY into the endothelial cell has recently been found and shown to be sodium and lysozyme dependent (Jiang et al 2007) and this explains how HCY can enter endothelial cells and become incorporated into proteins (Jakubowski et al, 2000). It is not known whether such mechanisms exist for non-endothelial cells, in particular for alveolar epithelial cells.

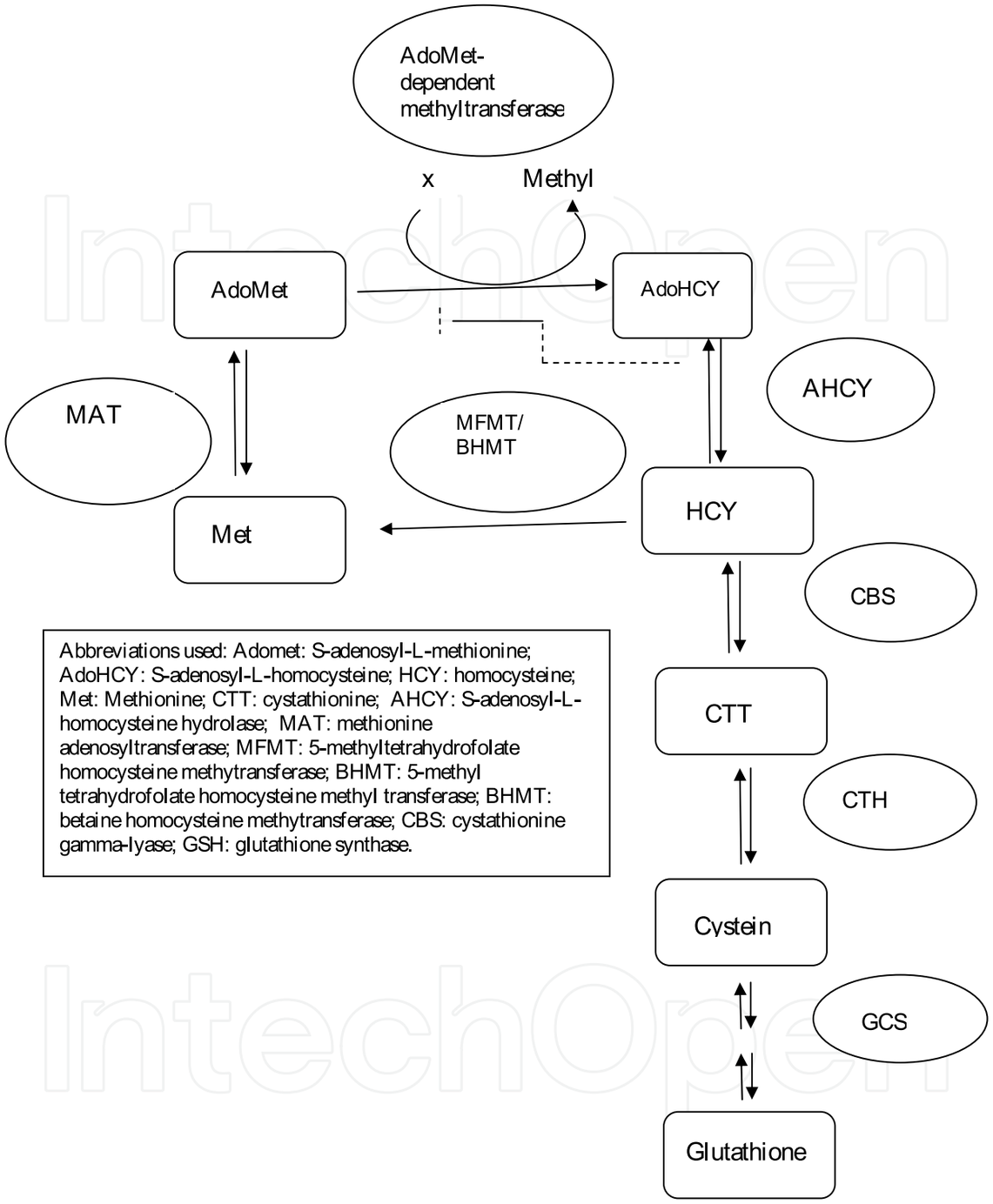



Fig. 1. Modified from Tehlivets (2011). The Figure shows the linkage between HCY and glutathione.

## 3. Measurements of homocysteine

Human plasma contains both free homocysteine (HCY) and its oxidised form, homocystine (HCY-HCY), where two molecules are bound via a disulphide bond. About 99% of

homocysteine exists in the oxidised form in plasma. About 75% of total homocysteine is protein bound. Plasma HCY concentrations may be altered by several physiological factors: age, gender and body mass.

Kai et al and Fimognari et al measured HCY by high performance liquid chromatography with fluorescence detection and Seemungal et al used a polarization immunoassay technique (Kai et al 2006, Figmonari 2011). Though the techniques were different their results were similar and are compared below.

## 4. Why study homocysteine in the COPD patient?

Smoking is by consensus the most important risk factor in the development of COPD (GOLD 2010). Cigarette smoking causes elevation of plasma HCY (Bazzano et al 2003, Kai et al 2006) though the effect may be variable (Nygard 1998). Smoking is also a risk factor for the development of vascular disease and cessation of smoking contributes to cardiac risk reduction (Ford 2007). Several studies have linked and continue to link homocysteine with cardiovascular risk (Homocysteine Studies 2002, Givvimani 2011, and Tehlivets 2011). Since both cardiovascular disease and COPD share a common cause (Izquierdo et al, 2010) which itself causes hyperhomocysteinaemia, it is reasonable to expect that COPD should be associated with elevated HCY.

## 5. Homocysteine and COPD and oxidative stress

The first study to find a difference in homocysteine in COPD patients was reported by Andersson and colleagues (Andersson 2001). They examined the plasma from 19 patients with COPD and 29 healthy subjects. They found that total plasma homocysteine levels were higher in COPD than controls. But also that there was a decreased concentration of reduced glutathione and decreased reduced to total glutathione ration nine COPD. They speculated on a relationship between HCY as a surrogate marker of extracellular pro-oxidant activity and plasma homocysteine.

## 6. In vivo studies of homocysteine in COPD patients

Table 1 summarises the subject characteristics on patients in the three studies of lung function, COPD and homocysteine. All of the studies are relatively small but all involved a control arm of asymptomatic subjects. All are cross-sectional studies of COPD outpatients. The first study to link HCY and lung function in COPD was a Japanese study of Kai et al who measured lung function twice within a 1-year interval. In all studies post-bronchodilator FEV1 was measured though it is not clear whether this was done for the controls in the Fimognari et al study. Reversibility was measured only in the Kai et al study. Table 1 shows that the Seemungal et al study enrolled slightly younger patients than both other studies with the Kai et al study enrolling only males. The CRP in both Seemungal et al and Fimognari et al studies was measured using immunometric assays.

The BMI in the Kai et al study was low at 20 $kgm^{-2}$. Some of the controls, though asymptomatic, may have had abnormal lung function in the Kai et al and Seemungal et al studies as the Mean FEV1 was 76 to 83% but this is unlikely in the Fimognari et al study as the Mean FEV1was 104%. The Kai et al study had COPD patients with the more severe

| Variable | | Kai 2006 | Seemungal 2007 | Fimognari 2009 |
|---|---|---|---|---|
| Number | Controls | 23 | 25 | 29 |
| | COPD | 24 | 29 | 42 |
| Age | Controls | 66.4 | 64.8 | 70.6 |
| | COPD | 70.7 | 69.1 | 71.3 |
| % Males | Controls | 100 | 64 | 72.0 |
| | COPD | 100 | 79 | 85 |
| BMI ($kgm^{-2}$) | Controls | 24.2 | 27.4 | 28.1 |
| | COPD | 20.0 | 24.0 | 26.5 |
| HCY* (micro Mol/L) | Controls | 9.8 | 8.2 | 11.5* |
| | COPD | 12.0 | 12.0 | 13.9* |
| FEV1 (L) | Controls | 2.58 | 2.25 | N/A |
| | COPD | 1.12 | 1.43 | N/A |
| FEV1% | Controls | 83.3 | 76.1 | 104.5 |
| | COPD | 38.5 | 49.1 | 52.8 |
| FEV1/FVC% | Controls | 88.4 | 78.1 | 78.0 |
| | COPD | 42.7 | 53.1 | 53.0 |
| CRP (mg/L) | Controls | N/A | 0.89 | 2.3 |
| | COPD | N/A | 2.05 | 5.5 |

*Median Values only shown in paper.

Table 1. Comparison of Patient Characteristics in three Lung Function Studies in COPD (Data are expressed as means except where otherwise stated.)

COPD (Mean FEV1 38%) compared to Fimognari et al 53%. In the controls, the HCY levels appeared much lower in the Seemungal et al study than the others. The HCY levels in the COPD patients were identical in the Kai et al and Seemungal et al studies but higher in the Fimognari et al study though in the latter only medians are shown. Also, CRP levels were significantly lower in the Seemungal et al study than in the Fimognari et al Study.

The BMI in the Kai et al study was low at 20 $kgm^{-2}$. Some of the controls, though asymptomatic, may have had abnormal lung function in the Kai et al and Seemungal et al studies as the FEV1 was 76 to 83% but this is unlikely in the Fimognari et al study as the FEV1 was 104%. The Kai et al study had COPD patients with the more severe COPD (FEV1 38%) compared to Fimognari et al 53%. In the controls, the HCY levels appeared much lower in the Seemungal et al study than the others. The HCY levels in the COPD patients were identical in the Kai et al and Seemungal et al studies but higher in the Fimognari et al study though in the latter only medians are shown. Also, CRP levels were significantly lower in the Seemungal et al study than in the Fimognari et al Study.

In conclusion there are differences in the patients between the three studies that make it difficult to actually compare *all* of the findings.

## 7. Homocysteine, lung function and lung function decline

The major manifestation of airflow obstruction in COPD is reduced maximum expiratory flow and slow forced emptying of the lungs (FEV1) and these features do not change

markedly over months (GOLD 2010). Most of the lung function impairment is progressive and thus rate of decline in FEV1 is an important outcome measure in COPD. COPD may be accompanied by airway hyperactivity and partial reversibility which when present increases the variance in FEV1 and FVC measurements. To eliminate this all three studies used post-bronchodilator lung function measurements (Kai et al 2006; Seemungal et al, 2007; Fimognari et al,2009).

All three studies agree that HCY is higher in COPD patients than in controls (Kai et al, 2006; Seemungal et al, 2007; Fimognari et al, 2009). But only one study found that HCY was higher in the more severe COPD (please see Figure 2) (Seemungal et al, 2007). Kai et al found that HCY was higher in patients with a higher FEV1 – an opposite finding to the Seemungal et al group.

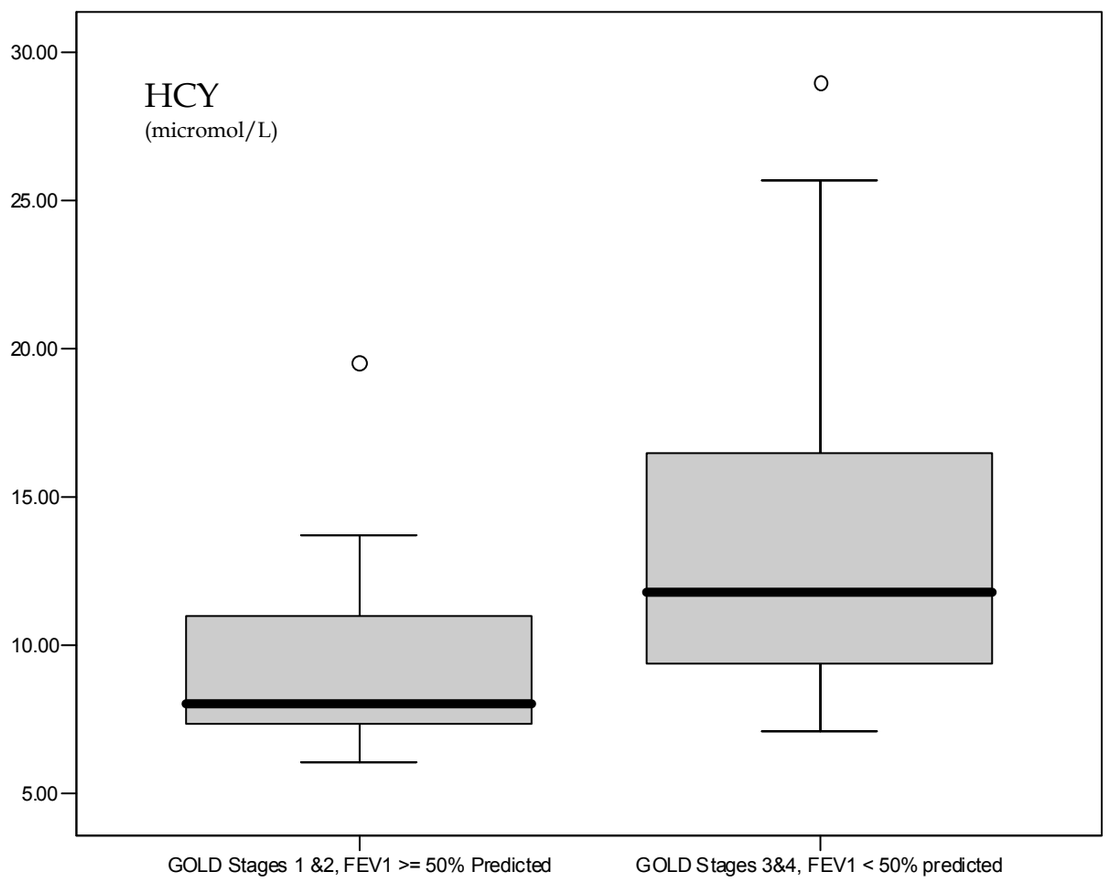



Fig. 2. Homocysteine and COPD severity based on Seemungal et al, 2006.

Kai et al are the only group so far to look at annual decline in FEV1 and HCY. In this study FEV1 decline varied between 0 ml/year and 275 ml /year. However the correlation was positive (r=0.40 and p-value = 0.02), that is, a high HCY was related to a more rapid decline in lung function. The authors have not explained the apparent contradiction between their findings in the cross-sectional analysis (of low HCY related to low lung function) and the paired analysis where FEV1 decline was faster in those with high plasma homocysteine (Kai

et al, 2006). Rather, the relationship with annual decline in FEV1 would appear to support the conclusion of Seemungal et al that COPD severity is related to a higher HCY (Seemungal et al, 2007).

In a subset analysis of the COPD-only group, Kai et al found that those with FEV1 less than 30% (N = 7) had a lower arterial oxygen tension and lower HCY than those with FEV1 greater than 60% (N = 8) – a very small sample in an already small study. However in the entire COPD sample there was no significant correlation between arterial oxygen tension and HCY. Kai et al used this finding to hypothesize that (a) hypoxia could easily occur on exertion in the patients with severe COPD and that (b) there is a possibility that hypoxia played a role in the reduction of the plasma HCY concentration via down regulation of methionine adenosyltransferase gene transcription. The difficulty with this hypothesis is that it is based on a very small subset difference in an already small study (Kai et al, 2006).

## 8. Homocysteine and CRP: Evidence for immune activation?

Serum C-reactive protein (CRP), is a ubiquitous marker of systemic inflammation, mortality and hospitalisation in COPD (Dahl et al, 2007; Man et al, 2004), cardiac disease in COPD (Sin et al, 2003) and of cardiac disease in the elderly (Zakai et al, 2007). High CRP levels have also been shown to correlate with low 6-min walk test scores (de Torres et al, 2007).

As shown in Table 1, both Seemungal et al and Fimognari et al measured serum CRP in their normal and COPD subjects and though their samples showed significantly different values for mean CRP, they both agreed that CRP was elevated in the COPD subjects compared to asymptomatic controls. The CRP levels in the normal controls in the Seemungal et al study was similar to that in previously published American and Dutch controls (Broekhuisen et al, 2005; Sin & Man 2003) and the greater value of CRP in COPD in the Seemungal et al study is the same as that attributed to COPD by Gan et al in their metaanalysis (Gan et al, 2004).

The Seemungal et al study found a correlation between CRP and HCY which was not found (rho= 0.377, p = 0.005) in the Fimognari et al study. The clinical implication of this finding from the Seemungal et al study is unclear at present more so because it was not supported by the Fimognari et al study. However, a similar correlation between HCY and CRP (as observed by Seemungal et al) has been reported in psoriatic arthritis (Sattar et al, 2007), in cancer (Schroecksnadel 2007) and in elderly patients with cardiovascular disease and dementia (Ravaglia et al, 2004). Taken together these results suggest that HCY may play a role in immune activation in some chronic diseases (Schroecksnadel et al, 2007) and its relationship to HCY in COPD may be a further indicator of the role of HCY in oxidative stress in COPD (Folchini et al, 2011).

## 9. Homocysteine and quality of life

The St. Georges Respiratory Questionnaire (SGRQ) (Jones et al, 1992) assesses quality of life in three domains: symptoms, activities and impacts. Scores in three domains are combined to give weighted average called the total score (Jones et al, 1992). The SGRQ has been shown to be sensitive to different levels of health (Jones 1997). As a standardised questionnaire the SGRQ has the advantage of allowing direct comparison between different patient

populations and treatment groups and has been shown to be responsive when used for these comparisons (Jones et al, 1991; Jones & Lasserson, 1994). The Symptoms score assesses the degree of distress due to frequency and severity of respiratory symptoms, whilst the impacts component addresses psychosocial effects (Jones & Booth 1997).

Of the three studies, only the Seemungal et al study assessed quality of life via the St. Georges Respiratory Questionnaire (SGRQ) in the COPD subjects. All of the quality of life indices (total, symptoms, impacts and activities) were related to HCY levels with a minimum correlation of: symptoms score 0.295, impacts score 0.330 and total score 0.289. The activities score was the only component not related to HCY. The HCY scores were higher in patients with worse quality of life scores – consistent with the relationships found between FEV1 and HCY (Seemungal et al 2007). The SGRQ scores have been shown to be an important outcome measures in COPD and predict frequent exacerbations and hospitalisation (Seemungal et al, 1998; Wilkinson et al, 2004). Though few serum parameters have been shown to predict exacerbations apart from CRP (Dahl et al 2007), the relationship between HCY and SGRQ does raise intriguing possibilities. This is the only result so far available for HCY and life style in COPD, HCY has been related to life style determinants in cardiac disease (Nygard et al, 1998). Further the relationship of elevated CRP to ten year mortality in COPD (Dhal et al 2007) and of HCY to mortality in coronary artery disease (Nygard et al, 1997; Ford et al, 2007) raises the issue of whether HCY is also related to mortality in COPD which would only be revealed by long term studies of COPD.

## 10. Effects of diet, renal disease on homocysteine – Other diseases

Kai et al did not assess dietary indices. Prior studies have all found that low vitamin B12 and or folic acid are related to hyperhomocysteinaemia (D'Angelo et al, 1997; Clarke et al, 2003; Kluijtmans et al, 2003). Seemungal et al estimated dietary intake of vitamins using the food frequency questionnaire and found no relation to plasma HCY values but Fimognari et al estimated serum vitamin B12and folic acid levels directly. The Fimognari et al study also attempted to determine if there was a role for co-morbidities in the elevation of HCY in COPD. Thus they attempted to control for those factors known to be associated with hyperhomocysteinaemia such as vascular disease, renal disease and diabetes (Dominguez et al, 2010; Austen et al 2003). When they controlled for these factors in a multivariate analysis in the COPD patients only, they found that the best predictors of high HCY were low serum folic acid, vitamin B12 and triglycerides. This has been supported by further work from the Andersson et al group (Andersson et al, 2007)

Fimognari et al did not measure vitamin B6 levels. Further these multivariate analysis, did not include the normal subjects therefore did not include COPD as a factor even though a prior analysis of all subjects in the Fimognari et al study had shown a relationship between both presence of COPD as well as FEV1% and HCY. It is therefore not clear whether a repeat analysis using all subjects in the study with COPD and FEV1% as independent variables would have yielded significant relationships with three B vitamins.

## 11. Homocysteine elevation in COPD: Pathogenesis or epiphenomenon?

Three studies shave shown that HCY is elevated in COPD relative to asymptomatic controls. The Kai et al study showed that COPD patients with a high HCY were likely to have faster

decline in FEV1. Seemungal et al showed that HCY was related to COPD severity. Taken together these results suggest that HCY is involved in COPD pathogenesis. In 2001 Andersson et al showed that HCY was elevated in COPD and that patients with high HCY were more likely to have a low reduced GSH and low GSH:GSSG ratio (Andersson et al, 2001; Sibrian-Vazquez et al, 2010). Further there is evidence from a laboratory study that low levels of reduced glutathione are associated with emphysema in the rat (Hamlet et al, 2007). These studies suggest that HCY is involved in redox pathways in COPD and that a high HCY reflects an imbalance in the redox state favouring oxidative stress. However only cohort studies will allow us to determine which comes first the oxidative stress or the elevation in HCY.

## 12. Implications for management

The implications for management of COPD are not yet known. However, for now, COPD patients with an elevated HCY should be screened for cardiac disease and more closely monitored for evidence of a faster decline in lung function. Investigations into the role of antioxidants that may effectively lower HCY are ongoing (Zinellu et al 2008).

## 13. Concluding comments

Homocysteine is a ubiquitous amino acid, elevation of which is associated with several diseases as diverse as thrombotic disorders and psoriasis. There is a strong link between cardiac disease and homocysteine levels. The cause and effects of HCY elevation in COPD are unknown but preliminary studies suggest that HCY is related to COPD pathogenesis and is likely to be associated with disorders in the redox pathway leading to oxidative stress in COPD. It is unknown whether HCY infiltrates the epithelium of the airway but HCY may well affect the endothelium of the lung.

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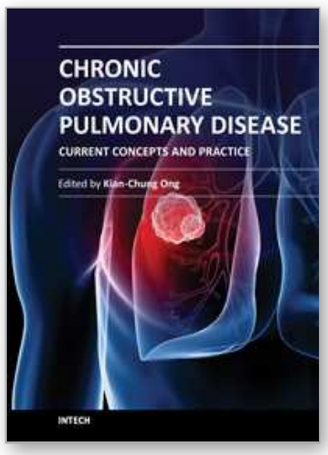
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**Chronic Obstructive Pulmonary Disease - Current Concepts and Practice**

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A decade or so ago, many clinicians were described as having an unnecessarily 'nihilistic' view of COPD. This has certainly changed over the years... This open access book on COPD provides a platform for scientists and clinicians from around the world to present their knowledge of the disease and up-to-date scientific findings, and avails the reader to a multitude of topics: from recent discoveries in the basic sciences to state-of-the-art interventions on COPD. Management of patients with COPD challenges the whole gamut of Respiratory Medicine - necessarily pushing frontiers in pulmonary function (and exercise) testing, radiologic imaging, pharmaceuticals, chest physiotherapy, intensive care with respiratory therapy, bronchology and thoracic surgery. In addition, multi-disciplinary inputs from other specialty fields such as cardiology, neuro-psychiatry, geriatric medicine and palliative care are often necessary for the comprehensive management of COPD. The recent progress and a multi-disciplinary approach in dealing with COPD certainly bode well for the future. Nonetheless, the final goal and ultimate outcome is in improving the health status and survival of patients with COPD.

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