The Healthy Obese Person

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Introduction

Obesity is one of the most important health-related problems facing humans today. Obesity is associated with increased mortality and morbidity through its association with cardiovascular disease [1], and a variety of related conditions such as Type 2 Diabetes Mellitus (T2D), musculoskeletal problems, various malignancies and Polycystic Ovary Syndrome [2]. The increasing prevalence of obesity is a global phenomenon that is showing no signs of abating [3]. Therefore, the public health implications of obesity and its pathological sequelae are set to become even more of a priority for future governments and health-care providers.

Much of the pathological sequelae of obesity stems from its association with metabolic dysfunction, including insulin resistance, dyslipidaemia, hypertension and dysglycaemia [4]. However, it is also well-recognized that an important sub-group of obese individuals do *not* manifest the typical metabolic dysfunction associated with human obesity, but rather are insulin sensitive and have a favourable metabolic profile [5]. The implication is that these individuals would therefore appear to be protected from future adverse cardiovascular events, although long-term prospective studies are required to confirm this assumption. The mechanisms that determine the metabolic fate of an obese individual are incompletely understood. It is clear however that identification of metabolically normal but obese individuals (MNO), or the â€˜healthy obese personâ€™, has clinical relevance: close observation and aggressive management of cardio-metabolic risk factors should be targeted towards those obese individuals who manifest metabolic *ab* normality.

In this chapter, we consider the prevalence of the MNO subgroup of obese individuals within our population. We then consider the phenotypic characteristics of the MNO subgroup, relating to physical activity and energy expenditure, visceral fat content and fat distribution, inflammatory profile, and sleep quality and duration. This section has been written to assist health-care professionals in the clinical identification of MNO individuals. A detailed discussion of the effects of endocrine dysfunction on human metabolic profile (for example hypogonadism in men) is beyond the scope of this article: we focus mainly on lifestyle effects on metabolism. However, it should be appreciated that there are numerous endocrine factors that may influence the expression of metabolic profile, and therefore affect metabolic phenotypic sub-group of obese

patients. We also discuss the appropriate diagnosis and management of MNO individuals based on the current literature.

Prevalence of obese but metabolically normal individuals

Some of our best data on the variability of metabolic profiles amongst obese people comes from the â€˜Brunek population-based study of atherosclerosis and its risk factorsâ€™, a study based in Italy by Bonora and colleagues [5]. This study included 888 adults (age range 40-79 years), who had been randomly selected for inclusion. Of these, 414 subjects were overweight or obese. In this study, 11% of the obese and overweight subjects fulfilled criteria for the MNO subgroup, with normal glucose tolerance, lipids, blood pressure and insulin sensitivity (measured with HOMA IR [6]). It has been suggested that if a younger group had been studied, then the proportion of subjects in the MNO sub-group may have been greater [7]. In a further 12%, metabolic profile was normal other than insulin resistance [5]. In a further study by Brochu and colleagues on 43 obese post-menopausal women (obesity defined on the basis of body fat >35%), it was demonstrated that 17 (40%) were in the MNO sub-group [8]. Other studies suggest that the MNO sub-group may form 20-30% of the obese population [9-11].

There are relatively few studies reported in the literature on the metabolic variability of obese subjects. Our best estimate for the prevalence of the MNO sub-group is that it forms a significant minority of the obese adult population, perhaps between 10% and 40%. However, this figure is likely to be influenced by the characteristics of the population studied including sex, age, ethnicity and lifestyle.

Characteristics and determinants of obese but metabolically normal individuals

i) Physical Activity and Energy Expenditure

Physical activity in humans is influenced by a number of factors. In recent years, our environment has become transformed, with technology enabling humans to expend much less energy in activities of daily living, transport being one examples of this. Future advances in technology are likely to further reduce the need for human expenditure of energy. It is well-established that physical inactivity over several years is detrimental to health, and is associated with a significantly increased risk for T2D, cardiovascular disease and premature mortality [12 , 13]. However, there is also evidence to suggest that cessation of physical activity even in the *short-term* is detrimental to health with association with increased intra-abdominal fat within 21 days in an animal model [14]. In a randomized controlled trial (Studies Targeting Risk Reduction Intervention through Defined Exercise [STRRIDE]) by Slentz and colleagues, it was demonstrated clearly through comparison of exercise training and control groups, that the *inactive* control group manifested metabolic deterioration and a sizeable *increase* in visceral fat mass even after 6-months [15 , 16].

The effect of exercise on visceral fat has been studied previously. In one study by Ross and

colleagues on overweight men, following a 12-week exercise program (to increase energy expenditure by 700kcal/day), weight loss was 7.5kg and cross-sectional area of visceral adipose tissue decreased by 52cm ^{2} [17]. In another study by Irwin and colleagues, a 12-month exercise program in overweight post-menopausal women (at least 45 minutes of moderate-intensity exercise for 5 days of the week), there was 8.5cm ^{2} loss of visceral fat area and 1.3kg reduction in body weight [18]. The data in the literature, including data from STRRIDE [16] suggest that there is a dose-response relationship between the amount of physical exercise and change in visceral fat content [15]. A further observation to support a link between exercise and visceral fat is the description of Japanese Sumo wrestlers undergoing intensive exercise, who despite gross obesity have normal amounts of visceral fat tissue and belong in the MNO subgroup [7 , 19]. On discontinuation of their strenuous training program, they develop features of the metabolic syndrome including markedly increased insulin resistance [7 , 19].

It is clear from the existing literature that physical activity significantly influences metabolic profile. There is some controversy regarding the actual mechanisms involved, although it seems likely that at least some of the relationship between exercise and metabolic profile is due to effects of exercise on visceral fat mass. Current literature does not support a preferential loss of visceral fat (versus subcutaneous fat) during exercise [15 , 16]. It is likely that exercise also has visceral-independent beneficial effects on metabolic profile. Maintenance of physical activity and exercise would appear to be metabolically-protective even in the context of obesity, and is likely to be a key factor in determining metabolic phenotypic sub-group including MNO.

ii) Visceral fat content and fat distribution

â€˜Obesityâ€™ is based on Body Mass Index (BMI) which in turn is influenced by total body fat mass. However, â€˜obesityâ€™ does not differentiate between different patterns of fat *distribution* , specifically the amount of visceral fat present (versus subcutaneous adipose tissue). â€˜Obesityâ€™ therefore encompasses a wide variety of fat distributions from predominantly gynoid (with fat distributed mainly on the hips and thighs) to predominantly android (with fat distributed more centrally within abdominal [including visceral] depots). It is likely that differences in visceral fat quantity between obese individuals underlie at least some of the variance in metabolic profiles amongst the obese population. Compared with total body fat, it is clear that visceral fat is a much better correlate with cardiometabolic risk factors such as triglycerides, HDL-cholesterol and blood pressure [15 , 20].

The causal relationships between visceral fat and cardiovascular risk factors are incompletely understood. However, important mechanisms include hepatic fatty acid infiltration and abnormal release of adipokines [15 , 21]]. Metabolic factors are important in the development of hepatic fibrosis associated with nonalcoholic steatohepatitis (NASH). The development of nonalcoholic fatty liver disease (NAFLD) as the hepatic manifestation of the metabolic syndrome is a complex process that may involve various nuclear receptors like peroxisome proliferator-activated receptor gamma (PPARÎ³), the endocannabinoid system and gut microbiota [22]. The initial part of this process, steatosis is likely to represent a means of storage of free fatty acids. Once the lipid storage threshold is exceeded, lipotoxicity may ensue [22]. Inter-individual variations in adipose tissue expandability may influence metabolic phenotype, including the expression of

the MNO subgroup in obese patients [22]. Variations in adipose tissue expandability in turn influence hepatic fatty acid infiltration and therefore insulin resistance. Alanine aminotransferase (ALT) has been shown to be a useful clinical marker of hepatic insulin resistance, demonstrating an inverse relationship with insulin sensitivity in a large group of non-diabetic individuals [23]. Raised ALT in an obese patient is therefore a sign of an adverse metabolic profile.

There is evidence to support the notion that *central* fat distribution is an important determinant of metabolic phenotype. The CASPIAN study included >4,800 children aged 6-18 years from Iran. In this large study, it was clearly demonstrated that phenotypically obese metabolically normal children tended to have *generalized* obesity whereas dysmetabolic features (dyslipidaemia, hypertension, metabolic syndrome) occurred more frequently in children with *central* (rather than generalized) obesity [24]. In this study, central obesity was not measured directly, but rather defined on the basis of waist circumference (which in turn is influenced by both visceral and abdominal subcutaneous fat depots). *Direct* measurement of visceral fat requires imaging such as MRI. There is also evidence to suggest that waist circumference is a better correlate of subcutaneous than visceral adipose tissue content at least in adults [25]. However, it is also widely-accepted that waist circumference is a useful clinical surrogate marker of visceral fat content. In a further study of 39 obese women (BMI 31-67kg/m ^{2}) that employed magnetic resonance imaging (MRI) to measure intra-abdominal fat, it was demonstrated that those women with a healthy metabolic profile (based on blood glucose, lipids and blood pressure) had lower intra-abdominal fat volume than those obese women with a metabolic abnormality [26]. Interestingly, there were no differences in subcutaneous fat volume between these two groups of women. Furthermore, intra-abdominal fat, insulin resistance and physical activity accounted for about one third of the variance of metabolic status amongst the obese women [26]. Finally, as alluded to above, Japanese Sumo wrestlers have normal amounts of visceral fat tissue and belong in the MNO subgroup, despite gross obesity [7 , 19].

Variance of visceral fat content within the obese population influences variance in metabolic profiles. Obese but metabolically normal individuals tend to have less visceral fat content than obese individuals with dysmetabolic features, and measurement of waist circumference therefore has clinical utility in the assessment of obese individuals. In addition to visceral fat content, it is likely that subcutaneous fat content influences metabolic profile. Inability to appropriately expand the subcutaneous fat depot may result in ectopic deposition of adipose tissue (including liver and muscle) with insulin resistance [27] Compared with *ob/ob* mice, morbidly obese transgenic mice that lack leptin but over-express adiponectin demonstrate improved insulin sensitivity, glucose and triglyceride levels [27]. It has been proposed that adiponectin acts as a peripheral starvation signal that promotes storage of triglycerides within adipose tissue thereby reducing ectopic adipose tissue deposition and improving insulin sensitivity [27]. In humans, there is evidence to show that subcutaneous gluteofemoral fat enables long-term entrapment of excess fatty acids thereby providing protection from the adverse metabolic effects of ectopic fat deposition [28].

iii) Inflammatory profile

Obesity tends to be associated with an inflammatory state. Release of pro-inflammatory

adipokines such as C-reactive protein (CRP), Tumour Necrosis Factor-Î± (TNF- Î±), Î±-1 antitrypsin and resistin, together with reduced secretion of adiponectin from adipose tissue (in particular the visceral fat depot) is likely to play an important role in the development of obesity-associated inflammation. Release of adipokines is also associated with insulin resistance [29] and cardiovascular disease [30], and it is likely that inflammation (including *vascular* inflammation) is implicated in these processes. Given the importance of inflammation in influencing metabolic profile, it is important to consider the inflammation profile of the MNO sub-group of obese humans.

Karelis and colleagues studied 88 obese and sedentary post-menopausal women, and defined the MNO sub-group (n=22) on the basis of the upper quartile of insulin sensitivity (determined by hyperinsulinaemic-euglycaemic clamp) [31]. The â€˜at riskâ€™ sub-group was defined by the lower quartile of insulin sensitivity. There were no differences between the MNO and at risk obese sub-groups for age, body weight, BMI and fat mass. However, there were significant differences between the two sub-groups in inflammatory profiles, with the MNO sub-group manifesting significantly lower high-sensitivity CRP and Î±-1 antitrypsin levels. The MNO sub-group also had significantly less visceral fat, lower fasting insulin and plasma triglycerides, and higher levels of high-density lipoprotein cholesterol than the at risk sub-group [31]. The authors concluded that a lower inflammation state may play a role in the metabolically-protective profile of the obese MNO sub-group [31].

There is a complex interplay between adiposity, fat distribution (in particular *visceral* fat), adipokine release and metabolic and inflammatory profiles. Cross-sectional studies reported in the literature do not enable causality to be determined, but rather show *associations* . In the study by Karelis and colleagues, it was noted that following adjustment for visceral fat, the significant differences in CRP between the MNO and at risk obese sub-groups disappeared [31]. It is possible therefore, that some of the adipokines measured may simply reflect visceral fat mass rather than playing an important causative role in the manifestation of abnormal metabolic and inflammatory states. Regardless of the mechanisms however, it seems clear from the literature that in addition to manifesting a normal metabolic profile, the MNO sub-group of obese humans also have a relatively normal inflammatory profile, which is presumably protective for future cardiovascular events.

iv) Sleep quality and duration

It is clear from a number of studies (>65 in the current literature) that there is a significant association between reduced sleep duration (<6 hours per night) and increased rates of obesity in both adults and children [32]. There is also evidence to implicate restricted sleep duration on abnormal appetite regulation (including decreased leptin and increased ghrelin levels) [33 , 34]. Several large studies have shown an association between impaired sleep and the development of T2D or impaired glucose tolerance [32]. Self-reported short sleep durations (or poor sleep quality) have been shown to be associated with hypertension (and higher blood pressure) [35 , 36]. It is well-established that reduced sleep duration (and impaired sleep quality) is independently associated with reduced insulin sensitivity [37]: reduced sleep duration for even one night has been shown to induce insulin resistance in healthy adult

humans [38]. There may even be a link between sleep duration and visceral fat accumulation [39].

It is clear from the current literature that sleep quality and duration appears to associate with a variety of metabolic parameters in humans (including obesity and appetite, glycaemic control, blood pressure and insulin sensitivity). Furthermore, use of Continuous Positive Airways Pressure (CPAP) treatment in patients with Obstructive Sleep Apnoea (OSA) improves metabolic profile [40]. It would appear that optimal sleep duration in human adults (7-8 hours) and good sleep quality are metabolically-protective. Therefore, one would expect that optimal sleep duration and quality in the context of obesity would associate with the MNO sub-group, although current data on this are lacking.

v) Genetics of the MNO sub-group

Although there are limited published data on the genetic determinants of the MNO subgroup, there are a number of published candidate gene studies on fat (including visceral fat) distribution that are summarized here. Data from the Quebec Family Study on 666 subjects showed that gene variants within plasminogen-activator inhibitor-1 (*PAI-1*) were associated with BMI and body fat mass [41]. Furthermore, certain variants within *PAI-1* (including the *PAI1* -675 4G/5G promoter polymorphism) were shown to associate with increased visceral fat around the time of menopause in women [41]. Other data on 759 participants from the Quebec Family Study showed that variants within the adiponectin gene (*ADIPOQ*) influence both overall and abdominal obesity [42]. In a further study, data from the HERITAGE Family Study suggested a role for variants within the alpha 2-adrenergic receptor gene (*ADRA2A*) for a propensity to store intra-abdominal fat independently of total body fatness [43]. Polymorphisms within the leptin receptor gene (LEPR) have also been shown to associate with abdominal fat in post-menopausal overweight women although there were relatively few subjects in this study (n=280) [44].

Genetic variants are likely to be implicated in the determination of metabolic phenotype in obese individuals, and there are many mechanisms by which such genetic variants may act. Although candidate gene studies would be useful, a genome-wide association study amongst phenotypic subgroups of obese subjects should be a focus for future research.

The outcomes of weight loss in obese but metabolically normal individuals

The aim of obesity management, particularly with drugs or surgery, is to reduce the impact of co-morbid conditions on the life or well-being of the obese individual. Metabolic and cardiovascular diseases are an important consideration because they are reversible with weight loss. Given that the MNO sub-group of obese individuals manifest by definition, a normal metabolic profile, the question arises regarding the appropriateness of weight loss in this sub-group. It might be inferred that MNO may not benefit as much from weight loss as those obese patients with evidence of metabolic de-compensation. Indeed, most guidelines for bariatric surgery prioritize

those obese patients with clear evidence of co-morbidities. However, further study is required to investigate the benefits of weight loss for the MNO sub-group in terms of long-term cardiovascular risk, mortality from cancers, morbidity related to musculoskeletal disease and psychological illnesses.

The data in the literature on this topic are controversial. In one large study by Sesti and colleagues, the effects of weight loss following insertion of a laparoscopic adjustable gastric band (LAGB) in 190 morbidly obese non-diabetic subjects was reported [45]. Those patients with a baseline insulin sensitivity index in the upper quartile were defined as MNO, and this sub-group was compared with the insulin resistant obese (IRO) patients, defined as baseline insulin sensitivity index in the three lower quartiles. At baseline, the IRO subjects had a higher BMI than the MNO subjects. At follow-up, six months post-LAGB insertion, BMI was significantly reduced in both sub-groups by equivalent amounts, the MNO and IRO sub-groups having 14% and 13% reductions in BMI at 6-months respectively [45]. It was demonstrated that metabolic indices such as fasting glucose and insulin, triglycerides, AST and ALT all showed significant reductions and HDL cholesterol increased in both the MNO and IRO sub-groups following weight loss at 6-months post-LAGB insertion. Although insulin sensitivity also improved in both sub-groups at 6-months, the percent change was greater in the IRO sub-group [45].

In three studies, the effects of weight loss following lifestyle (including dietary) changes were reported. These showed no change in metabolic profiles in the MNO subjects despite significant weight loss [46-48]. In one study, an improvement in metabolic profile in the MNO sub-group following lifestyle intervention was reported [49]. It has been suggested that one explanation for the differences in metabolic profile response to weight loss in the MNO sub-group post-LAGB insertion versus lifestyle change, is that the amount of weight lost is usually much greater following LAGB insertion compared with lifestyle change [45]. Given that improved insulin sensitivity is correlated with reduction in BMI, there may need to be a critical amount of fat mass reduction in the MNO sub-group to effect a beneficial influence on metabolic profile [45].

How should we reconcile the controversy in the current literature regarding the metabolic effects of weight loss in the MNO sub-group? Although modest weight loss through dietary and lifestyle change may not be sufficient to effect a significant improvement in metabolic profile in this sub-group, it seems clear that further reductions in fat mass following LAGB-insertion does indeed improve metabolic profile further. Therefore, metabolic normality in an obese patient should *not* be used as a reason to avoid bariatric surgery. Furthermore, given the multitude of beneficial effects of improved diet and lifestyle and weight loss in obese patients (independent of improved metabolic profile), we would argue that obese patients should be advised to lose weight, *regardless* of their metabolic profile.

How should we diagnose and manage obese but metabolically normal individuals?

The diagnosis of the MNO subgroup is usually achieved pragmatically in clinical practice. Absence of Diabetes or glucose intolerance, Non-Alcoholic Steato-Hepatitis (NASH), hypertension or dyslipidaemia in an obese patient suggests the diagnosis. However, it is

important to standardize criteria for MNO for research purposes. Sims has suggested that diagnosis of the MNO subgroup of obese individuals should be based on four factors: i) family history of early-onset obesity with relative absence of features of metabolic syndrome; ii) no evidence of the features of metabolic syndrome; iii) universal distribution of body fat without *visceral* abdominal accumulation; iv) normal insulin sensitivity [7] . Measurement of insulin sensitivity can be performed with a variety of techniques, the gold-standard being the euglycaemic-hyperinsulinaemic clamp [50]. However, this technique is time-consuming and relatively expensive, and therefore more suitable for research studies. An alternative means of estimating insulin sensitivity is the Homeostasis Model Assessment of Insulin Resistance (HOMA2-IR) [6]. HOMA2 IR is based on serum fasting levels of glucose and insulin, and can be calculated using the Oxford Diabetes Trials Unit calculator available on the website, www.dtu.ox.ac.uk .

In clinical practice, it is important to have a practical means of assessing obese patients for metabolic phenotype. Precise and accurate measurement of visceral fat content requires expensive and time-consuming imaging protocols (including use of MRI) which would not be feasible for use in standard clinical practice. As an alternative, it is widely-accepted that waist circumference is a useful surrogate marker for visceral fat content, and is easily measurable in the clinical setting (mid-way between the iliac crests and the inferior rib margin). As an alternative, it has been shown that the â€˜hypertriglyceridaemic waistâ€™ phenotype (a combination of increased waist circumference and raised serum triglycerides) is a useful screening tool for clustering of metabolic abnormalities [51]. We suggest that waist circumference cut-offs be based on international diagnostic consensus of the definition of metabolic syndrome as proscribed by the International Diabetes Federation (IDF) [52]. The cut-offs for waist circumference as defined by IDF are ethnicity-dependent. For European women, the cut-off for waist circumference is â‰¥80cm, and for European men it is â‰¥94cm. In addition to a pre-requisite for waist circumference, IDF-defined metabolic syndrome is also based on the presence of at least two of the following criteria: (i) elevated triglycerides (â‰¥1.7 mmol/l); (ii) reduced HDL cholesterol (<1.29 mmol/l in women) or specific treatment for lipid abnormalities; (iii) elevated blood pressure (systolic BP â‰¥130mmHg or diastolic BP â‰¥85mmHg) or specific treatment of previously diagnosed hypertension; (iv) impaired fasting plasma glucose â‰¥5.6 mmol/l or previously diagnosed T2D [52]. Using waist circumference as a surrogate marker for visceral fat, HOMA2 IR (based on measurements of fasting glucose and insulin) as an estimate of insulin sensitivity, and the IDF-based criteria [52] for diagnosis of metabolic syndrome, it should be feasible to identify and diagnose the MNO sub-group of obese patients in the clinical setting.

Adolescence is a physiologically insulin-resistant state and a period of life where obesity can become clinically manifest. Unfortunately, the prevalence of obesity during childhood and adolescence has increased substantially over recent decades, and this trend is not showing any signs of abating. In one study on 861 obese children and adolescents, it was shown that NAFLD was an early mediator reflecting metabolic dysfunction [53]. In a further study it was shown that waist circumference was a useful predictor of components of the metabolic syndrome [54]. The predictors of the MNO subgroup during adolescence should be a focus for future research.

It is important to emphasize that obese patients within the MNO sub-group still require clinical

follow-up, and that exercise continues to be important . Although their current metabolic profile is normal, it seems likely that metabolic phenotype may change over time and that patients within the MNO subgroup may develop insulin resistance and features of the metabolic syndrome. However, it is clear that insulin sensitivity and other metabolic indices are influenced by factors such as physical activity, diet, age and sleep quality [7]. Any change in lifestyle of an obese patient is therefore likely to affect metabolic phenotypic subgroup, even if there is no appreciable change in weight. Therefore, we would argue that although active management of the obese MNO subgroup may not be required, close clinical follow-up of this subgroup is essential. At each clinical follow-up, assessments should include any changes in lifestyle and metabolic risk factors as outlined above, and these should be managed accordingly.

Conclusions

Human obesity, as with many other biological traits, is a heterogeneous phenomenon. Genetics plays an important role in determining the BMI of an individual, with the heritability of human obesity being approximately 0.7 [55 , 56]. (*FTO* is the first identified gene to be implicated in the development of common polygenic obesity [57]). It is also clear that environmental factors are important, particularly dietary factors and physical exercise. Other lifestyle factors like sleep quality and sleep duration are also known to affect appetite and weight [58 , 59], and this interplay of genetic and environmental factors is one explanation for the complexity of the pathogenesis of human obesity. Given such complexity, it is perhaps not surprising that the *phenotype* of human obesity is heterogeneous. Metabolic profile is an important aspect of human obesity phenotype, and one that presumably influences future cardiovascular risk. Although obesity is defined on the basis of BMI, variability of fat distribution is likely to play a key role in determining metabolic profile (including insulin sensitivity) with *visceral* fat preponderance being associated with metabolic dysfunction and insulin resistance. The mechanisms that determine body fat distribution are incompletely understood, although it is clear that sex differences pertain due to the known effects of sex hormones (such as estradiol and testosterone) on adipose tissue, with pre-menopausal women typically manifesting a gynoid fat distribution (fat predominantly located on the thighs and buttocks) and men typically having an android distribution (central/visceral fat predominance) [60]. Obese men are therefore more likely to manifest metabolic dysfunction compared with obese pre-menopausal women.

Although obesity is clearly a risk factor for metabolic dysfunction and insulin resistance, it should be appreciated that metabolic dysfunction is a separate entity to obesity. Given the scenario of generalized fat distribution and enhanced physical activity, it is possible to manifest a normal metabolic profile in the context of obesity (MNO phenotypic sub-group), and this metabolically normal subgroup represents a significant minority of obese patients. Although patients in the MNO sub-group do not require active management of cardiovascular risk factors, it is important for these patients to be followed-up closely given the lack of long-term data and the risk of development of metabolic dysfunction in any obese patient following any change in lifestyle (including diet, exercise and sleep quality and duration).

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