**UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL**

**FACULDADE DE MEDICINA**

**PROGRAMA DE PÓS-GRADUAÇÃO EM PSIQUIATRIA E CIÊNCIAS DO COMPORTAMENTO**

**TESE DE DOUTORADO**

# ASSOCIAÇÃO ENTRE ESTADO NUTRICIONAL, NÍVEIS SÉRICOS DE LEPTINA E GRAVIDADE DO USO DE CRACK

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Porto Alegre

Dezembro de 2017

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Tese de Doutorado a ser apresentada ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento como requisito parcial à obtenção do título de Doutor em Psiquiatria e Ciências do Comportamento.

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CIP - Catalogação na Publicação

Escobar, Mariana
ASSOCIAÇÃO ENTRE ESTADO NUTRICIONAL, NÍVEIS SÉRICOS DE LEPTINA E GRAVIDADE DO USO DE CRACK / Mariana Escobar. -- 2017.
53 f.
Orientador: Flavio Pechansky.

Coorientador: Lisia Von Diemen.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, Porto Alegre, BR-RS, 2017.

1. Crack. 2. Gravidade do uso de crack. 3. Leptina. 4. Estado Nutricional. 5. Biomarcadores. I. Pechansky, Flavio, orient. II. Von Diemen, Lisia, coorient. III. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

“Seja sempre alegre. Estudando e trabalhando com alegria, você progredirá cada vez mais.”

**Masaharu Taniguchi**

**DEDICATÓRIA**

Ao meu filho, Theo Escobar Azambuja, que a cada dia me ensina, me fascina e me encanta com sua alegria e curiosidade em aprender.

## AGRADECIMENTOS

A minha Família, em especial a minha mãe, pelo apoio logístico e emocional, sempre;

Ao meu marido Daniel Sampaio de Azambuja, pelo amor e parceria;

Ao meu filho Theo Escobar Azambuja, meu maior projeto e presente desta vida, que com tão pouca idade já demonstra os sentimentos mais generosos que alguém pode ter;

Ao Prof. Dr. Flavio Pechansky e a Prof. Dra. Lísia Von Diemen, pela oportunidade, paciência, orientação e confiança;

A Prof. Dra. Martine Elisabeth Kienzle Hagen pelo apoio técnico;

À banca, Prof. Dr. Pedro Vieira da Silva Magalhães, Prof. Dra. Ana Breatriz Cauduro Harb, Dra. Michelli Cristina Silva de Assis e Dra. Thais Ortiz Hammes, pela honra em tê-los avaliando meu trabalho;

Aos participantes deste estudo, que em um momento delicado de sua trajetória se disponibilizaram a participar desta pesquisa;

Aos colegas e Amigos do Centro de Pesquisa em Álcool e Drogas (CPAD);

À equipe da Unidade de Adição da Álvaro Alvim (UAA), pela colaboração com as coletas;

Aos amigos que conheci na UAA e no CPAD e que levo para vida: Alessandra Calixto, Lucas França Garcia, Charlise Pasuch de Oliveira, Mitieli Vizcaychipi Disconzi, Cassio Lamas, Márcia da Silva Vargas, André Lopes, Felipe Ornell e Silva Halpern;

As minhas colegas e amigas da sala 639, Carla, Elaine, Lívia, Luciana e Nícia pelo acolhimento e convivência diária;

Ao Luciano Guimarães pela parceria e dedicação nas análises estatísticas;

A Cassia Medino Soares, pela dedicação na coleta dos dados;

A Dra. Juliana Nichterwitz Scherer, meu agradecimento especial, pela dedicação, sugestões, revisões e parceria na redação dos artigos desta tese;

A Melissa Quintana Huf e Cláudia Grabinski, pelo apoio administrativo e disponibilidade;

Ao Grupo de Pesquisa e Pós-Graduação (GPPG) do HCPA, pela agilidade e parceria em todos os serviços solicitados e prestados, em especial: Rosa Maidana, Roberto Silva e Marta Dotto;

Ao Hospital de Clínicas de Porto Alegre, por oportunizar conciliar pesquisa à prática clínica e por financiar este projeto através do Fundo de Incentivo à Pesquisa e Eventos (FIPE).

## RESUMO

O Crack atua como um potente estimulante do sistema nervoso central, bloqueando a recaptação pré-sináptica de noradrenalina e dopamina, produzindo alto nível destes neurotransmissores nos receptores pós-sinápticos, ocasionando efeitos de prazer. O uso de drogas e a vulnerabilidade social podem resultar em desnutrição, causando danos à saúde. Além disso, peptídeos relacionados com o apetite podem estar regulando o uso de drogas. A leptina, um peptídeo produzido principalmente pelo tecido adiposo, informa ao cérebro a presença de energia, induzindo o bloqueio do neuropeptídio Y (NPY), diminuindo o apetite. Nossa hipótese é que a leptina possa estar regulando, além da ingestão de alimentos, o consumo de drogas. Não existem estudos na literatura sobre o estado nutricional de usuários de crack (com métodos bioquímicos e antropométricos), nem pesquisas que avaliam a relação da leptina com a gravidade do uso da droga. Assim, o objetivo desta tese foi avaliar o estado nutricional e os níveis séricos de leptina em usuários de crack e suas correlações com variáveis antropométricas, bioquímicas e gravidade de consumo da droga (crack). O artigo 1 da presente tese é uma análise transversal de 108 usuários, onde avaliamos o índice de massa corporal (IMC), composição corporal por bioimpedância (BIA), parâmetros bioquímicos e correlacionamos com a gravidade do uso da droga. O artigo 2 compreende uma análise dos níveis séricos de leptina, e suas correlações com IMC, BIA e gravidade do uso de crack em 40 indivíduos. Como principal achado do artigo 1, demonstramos que maioria dos indivíduos possui um IMC dentro da normalidade, no entanto, as análises bioquímicas indicaram alterações, mostrando que, embora os usuários de crack não possuam baixo peso, apresentam outras deficiências nutricionais específicas. No artigo 2, sugerimos que a leptina possa estar envolvida com a gravidade do uso de drogas, talvez em uma forma similar à modulação da ingestão de alimentos.



**Palavras Chave:** Crack. Biomarcadores. Leptina. Estado Nutricional.

## ABSTRACT

Crack is a potent central nervous system stimulant, inhibiting the presynaptic reuptake of noradrenaline and dopamine, producing high levels of these neurotransmitters at postsynaptic receptors, causing pleasure effects. Drug use and vulnerability can lead to malnutrition, causing a number of health consequences. In addition, appetite-related peptides may be regulating drug use. Leptin, a peptide produced primarily by adipose tissue, communicates the brain about energy reserves, inhibiting NPY and decreasing appetite. Our hypothesis is that leptin may be regulating, in addition to food intake, drug use. There are no studies that report crack users nutritional status (with biochemical and anthropometric methods), or about the relationship between leptin and the severity of drug use. Thus, the objective of this study was to evaluate the nutritional status and leptin serum levels, in crack users, and its correlations with anthropometric, biochemical and crack severity variables. The article 1 of the present study is a cross-sectional analysis, about nutritional status of 108 users. We evaluated BMI, body composition, biochemical parameters and correlated with the severity of drug use. Article 2 is a study about serum levels of leptin, and its correlations with BMI, BIA and severity of crack use in 40 individuals. As the main finding of article 1, we demonstrated that most individuals have a BMI within the normal range, however, biochemical analysis indicated below-expected parameters, showing that, Crack users are not underweight but have other specific nutritional deficiencies, which are also considered malnutrition. In paper 2, we suggest that leptin may be involved in the severity of drug use, perhaps in a similar way to food intake signaling.



**Keywords:** Crack. Biomarkers. Leptin. Nutritional Status.

## LISTA DE ABREVIATURAS

**AGRP:** Agouti Related Protein / Peptídio Relacionado ao Agouti

**AND:** Academy of Nutrition and Dietetics

**ASPEN:** American Society for Parenteral and Enteral Nutrition

**BIA:** Bioimpedância Elétrica

**BMI:** Body Mass Index

**CCK:** Colecistoquinina

**CPAD**: Centro de Pesquisas em Álcool e Drogas

**CT:** Colesterol Total

**ELISA**: Enzyme Linked Immuno Sorbent Assay

**FIPE:** Fundo de Incentivo a Pesquisa e Eventos

**GABA:** Acido Gama Aminobutírico

**GLP1:** Glucagon Like Peptide-1 / Peptídeo Semelhante a Glucagon 1

**HCPA:** Hospital de Clínicas de Porto Alegre

**HDL:** High Density Lipoprotein/ Lipoproteína de Alta Densidade

**HIV:** Human Immunodeficiency Vírus / Vírus da Imunodeficiência Humana

**IMC:** Índice de Massa Corporal

**LDL:** Low Density Lipoprotein / Lipoproteína de Baixa Densidade

**NPY:** Neuropeptídio Y

**OMS:** Organização Mundial da Saúde

**PYY:** Peptídeo YY

**SNC:** Sistema Nervoso Central

**SPA:** Substâncias Psicoativas

**SPSS:** Statistical Package for Social Sciences

**TCLE:** Termo de Consentimento Livre e Esclarecido

**WHO**: World Health Organization

## LISTA DE TABELAS

### Tabelas Artigo 1



### Tabelas Artigo 2

**SUMÁRIO**

# 1 INTRODUÇÃO

## 1.1 Substâncias psicoativas: Crack

O crack é uma substância estimulante, derivada da cocaína (extrato alcaloide da folha da planta *Erythroxylon Coca)*, bicarbonato de sódio ou amônia e um solvente como éter ou acetona, é comercializado na forma de pedras porosas e pode ser fumado, o nome popular "crack" é proveniente do ruído produzido por essas pedras durante o aquecimento (1-4). A administração fumada da cocaína tem um início de ação mais rápido (a sensação de prazer é percebida quase que instantaneamente - 10 a 15 segundos) e o tempo de efeito é mais curto, tem curta duração, de 5 minutos em média, quando comparado a qualquer outra forma de administração, essa característica leva o usuário a desenvolver dependência mais rapidamente. Os usuários, de uma forma geral, possuem um perfil associado a comportamentos violentos e ao crime, e com relação à saúde, apresentam morbidades clínicas e psiquiátricas (2, 5).

Pesquisas epidemiológicas demonstram que o uso de crack, muitas vezes, inicia-se na infância e na adolescência, devido à facilidade de acesso e antecedido ao consumo de outras drogas, como por exemplo, o álcool, o tabaco e a maconha (2, 3, 5, 6). O Brasil é considerado o maior consumidor mundial de crack, com aproximadamente 1,7 milhão de usuários regulares (1, 7). Estima-se que a prevalência do uso regular de crack ou similares nas capitais brasileiras seja de 0,81%, correspondendo a 35% dos consumidores de drogas ilícitas, excluindo a maconha (7). Apesar das taxas de consumo do crack serem inferiores a de outras drogas, a vulnerabilidade que envolve estes indivíduos faz com que muitos se exponham a outras situações de risco à saúde, além de ser a droga ilícita que mais conduz a internações em hospitais psiquiátricos e a que mais provoca demanda por atendimento, gerando um custo expressivo para o sistema público de saúde (8).

A cocaína/crack atua como um estimulante no sistema nervoso central (SNC), e no sistema de recompensa cerebral, bloqueando a recaptação pré-sináptica de noradrenalina e dopamina produzindo alto nível destes neurotransmissores nos receptores pós-sinápticos, ocasionando efeitos de prazer (9). O estímulo associado ao aumento de dopamina adquire um significado motivacional e emocional intensos, que resultam na busca excessiva pela substância. Este sistema de recompensa assegura comportamentos fundamentais à sobrevivência da espécie, tais como alimentação, exercício e sexo, sendo o uso de substâncias psicoativas (SPA) um ativador deste mecanismo. Dessa forma, aumenta a possibilidade de

que tais comportamentos sejam sempre repetidos, implicando no desenvolvimento da dependência. As situações “naturais” que normalmente estimulam o sistema de recompensa chegam a aumentar em até 100% sua atividade. Por sua vez, a ação de substâncias psicoativas como a cocaína e crack, chega a elevá-la em até 1000% (10-12).

O sistema de recompensa cerebral tem seu funcionamento principalmente por meio de duas estruturas: O sistema mesolímbico e o mesocortical. O sistema mesolímbico é composto pela área tegmental ventral, núcleo accumbens, amígdala e o hipocampo, e está relacionado ao mecanismo de condicionamento às emoções ligadas ao uso das SPA. O sistema mesocortical é composto pela área tegmental ventral, córtex pré-frontal, córtex órbito-frontal e giro do cíngulo, relaciona-se com os efeitos das SPA, como compulsão e perda do controle, é o principal sistema responsável pelo aprendizado, e está relacionado ao controle de impulsos e a tomada de decisões (13-17). A dopamina é o principal neurotransmissor presente no sistema de recompensa cerebral, porém não é o único responsável por sua ação. Neurotransmissores como a serotonina, noradrenalina, glutamato e o ácido gama aminobutírico (GABA) são responsáveis pela modulação do SNC e também estão presentes no sistema de recompensa (18-20).

## 1.2 Estado nutricional

Muitas morbidades estão associadas ao uso de crack. O estilo de vida vulnerável do usuário o expõe ao risco de desnutrição, propiciando o aparecimento de diversas doenças. Tanto os efeitos agudos como os crônicos podem ocasionar danos individuais ou sociais e prejuízos à saúde. A utilização de crack tem sido relatada por induzir perfurações intestinais, ulcerações gástricas, fibrose retroperitoneal, dor abdominal, náuseas, isquemia mesentérica e esofagite (21), prejudicando a digestão e absorção, podendo ocasionar deficiências nutricionais. Há a presença também de distúrbios metabólicos como hipoglicemia, acidose láctica e hipocalemia, prejudicando o metabolismo energético e o equilíbrio hidroeletrolítico (22, 23). As consequências clínicas sobre o uso de crack são descritas em vários estudos (2, 21, 24-26), no entanto, há uma lacuna na literatura sobre os aspectos nutricionais. A desnutrição em usuários de drogas é multifatorial e pode ser intensificada pelo baixo consumo calórico, função metabólica e gastrointestinal prejudicada, ou mesmo pelos efeitos deletérios da própria droga (27).

Segundo Vasconcelos (28), o estado nutricional de um indivíduo pode ser caracterizado como: “Condição de saúde, influenciada pelo consumo de nutrientes, identificada pela correlação de informações obtidas de estudos físicos, bioquímicos, clínicos e dietéticos”, assim o autor conceitua estado nutricional como a síntese orgânica das relações entre o homem, à natureza e o alimento, as quais se estabelecem no interior de uma sociedade, e o desequilibro destes fatores resulta em desnutrição (por carências ou excessos). A desnutrição tem sido descrita como o desequilíbrio entre ingestão e necessidade, que resulta em alterações metabólicas e funcionais importantes. No entanto, ainda não existe um critério internacionalmente aceito para o diagnóstico de desnutrição (29).

As terminologias em nutrição tem causado muita confusão, na língua inglesa existe uma nomenclatura mais clara e detalhada, ainda não utilizada de forma ampla e traduzida para português: “Malnutrition, undernutrition, depletion, wasting, cachexia” - são alguns dos termos utilizados para denominar a condição resultante das deficiências de macro e micronutrientes, do catabolismo das reservas de proteínas e energia devido à doença e ao envelhecimento. No entanto, há o entendimento tanto das sociedades internacionais como nacionais, da necessidade de padronização mundial destes termos (30).

Os prejuízos ao estado nutricional do indivíduo normalmente ocorrem ao longo de uma inadequação na ingestão, absorção e/ou transporte de nutriente, ocasionando alterações fisiológicas (31, 32), sendo um dos principais contribuintes para o aumento da morbidade e mortalidade, diminuição da função e qualidade de vida, aumento da frequência e duração da internação hospitalar e custos mais elevados de cuidados à saúde (33). A perda de peso pode ocorrer neste processo e os indivíduos podem apresentar condições inflamatórias, hipermetabólicas e hipercatabólicas associadas, alterando o funcionamento do organismo como um todo (29, 33, 34).

Efeitos secundários relacionados ao uso de drogas podem causar anorexia e/ou interferir na ingestão de alimentos. A diminuição da ingestão nutricional, o aumento das necessidades de energia e proteína e processos inflamatórios podem estar presentes em usuários de crack – e desenvolvem papel importante na recuperação do estado nutricional. Além das causas patológicas da desnutrição, fatores socioeconômicos, como baixa renda e vulnerabilidade social também podem contribuir para o desenvolvimento da desnutrição (35).

O diagnóstico da desnutrição geralmente é baseado em medidas objetivas do estado nutricional, incluindo avaliações da ingestão de nutrientes, dados antropométricos, exame físico e parâmetros bioquímicos (36). A Academy of Nutrition and Dietetics (AND) e a

American Society for Parenteral and Enteral Nutrition (ASPEN) recomendam que um conjunto padronizado de características diagnósticas seja utilizado para interpretar e documentar a desnutrição em adultos na prática clínica, estabelecendo como primeiro passo, antes do diagnóstico nutricional, uma avaliação da vulnerabilidade social e ambiental do indivíduo. Assim, as condições clínicas e sociais do usuário de crack deveriam integrar o instrumento de diagnóstico do estado nutricional (33).

Em um estudo com usuários de múltiplas substâncias, Sæland et. al., (37) relataram uma forte associação entre as concentrações de hemoglobina, ferritina sérica e albumina com baixo peso, demonstraram também, sinais clínicos de deficiência de micronutrientes em cerca de 70% dos indivíduos. A deficiência de vitaminas antioxidantes nesta população (usuários de múltiplas drogas) foi noticiada há alguns anos (38), demonstrando um desequílibro entre vitaminas antioxidantes e estresse oxidativo. Sæland et. al. (37), verificaram que o padrão de uso de SPA possui uma correlação inversa com o índice de massa corporal (IMC), e que o tempo de uso afetou os parâmetros nutricionais analisados (IMC, albumina, hemoglobina e ferritina). Recentemente, Ross et. al. (39) com uma população predominantemente de alcoolistas, demonstraram que 50% dos indivíduos eram deficientes em ferro ou vitaminas. Vários estudos mostraram desnutrição e baixo peso em usuários de múltiplas drogas (27, 38-43), por outro lado, o ganho de peso e a compulsão alimentar foram observados entre pessoas que se recuperam da dependência de drogas e álcool, sugerindo a possibilidade de que alimentos e as drogas estejam atuando pelos mesmos mecanismos de recompensa cerebral (42, 44-46).

Surpreendentemente, em um estudo piloto do nosso grupo, os usuários de crack apresentaram, em sua maioria, eutrofia e excesso de peso na admissão hospitalar (47). Este achado nos motivou a estabelecer mais variáveis de associação, para obtermos mais respostas quanto aos parâmetros bioquímicos no tratamento nutricional destes indivíduos. Além disso, há uma necessidade de compreender as percepções e comportamentos relacionados à alimentação no campo da dependência química. Em uma publicação recente Jeynes & Gibson (48) descreveram, em uma revisão narrativa, uma relação entre transtorno do uso de substâncias e nutrição e ressaltaram a necessidade de uma avaliação nutricional detalhada para determinar necessidades específicas de micronutrientes e uma sobreposição no sistema de recompensa cerebral, sugerindo uma ligação entre restrição alimentar, sinalização de saciedade e uso de drogas.

## 1.3 Biomarcadores: Leptina

Há a possibilidade de que peptídeos produzidos no tecido adiposo e intestino possam estar regulando o comportamento alimentar e o de uso de SPA, como por exemplo, a leptina, grelina, insulina e o NPY (49, 50). A ingestão alimentar, saciedade, apetite e compulsão são controlados por sistemas neuroendócrinos, recebendo sinais do sistema digestório e tecido adiposo, pela liberação de peptídeos reguladores do comportamento alimentar (adipocinas e incretinas) (9, 51, 52).

Volkow et. al. (50) sugerem a possibilidade de que alimentos e drogas de abuso possam estar atuando pelos mesmos mecanismos de recompensa cerebral. A compulsão, o descontrole alimentar e o uso de alimentos, em especial as gorduras e açúcares têm sido utilizados como possíveis substitutos de álcool e SPA em usuários em tratamento (9, 51, 52). Há a possibilidade de padrões alimentares, como a compulsão intermitente, possam desencadear mecanismos neurológicos de recompensa, produzindo uma maior tolerância para as SPA (37).

No cérebro, os três maiores componentes desse sistema são: o tronco encefálico, hipotálamo (centro integrador) e o córtex (órbitofrontal, núcleos da base, ínsula, sistema límbico, núcleo accumbens e complexo amigdaloide) (53). O hipotálamo, especificamente o núcleo arqueado e o complexo vagal dorsal do tronco cerebral, são as principais estruturas envolvidas no comportamento alimentar (53). No intestino delgado, a colecistocinina (CCK), sinaliza a saciedade, principalmente, pela presença de lipídios e proteínas. Nas porções mais baixas do intestino, o peptídeo YY (PYY) e o peptídeo semelhante ao glucagon (GLP-1), são secretados pela estimulação direta dos nutrientes na parede intestinal. Tanto PYY como o GLP-1 são anoréxicos. O GLP-1, produzido nas células do íleo, também funciona como um inibidor de apetite (54).

A grelina acilada atua no controle da ingestão de alimentos e balanço energético, reduzindo a oxidação de gorduras. Seus efeitos orexígenos são mediados por meio da ativação do neuropeptídio Y (NPY) e do peptídeo relacionado ao Agouti (AGRP) no núcleo arqueado do hipotálamo, que por sua vez aumenta a ingestão de alimentos. A grelina também regula a fome pré-prandial (55, 56). A leptina, produzida principalmente pelo tecido adiposo subcutâneo, informa ao cérebro a presença do excesso de energia (tecido adiposo), induzindo

bloqueio do NPY, suprimindo o apetite. Quando as reservas de gordura estão baixas, a diminuição de leptina estimula a produção de NPY com aumento do apetite. Além disso, a diminuição da secreção de leptina limita o gasto energético, reduzindo a secreção de hormônios tireoidianos e de gonadotrofinas e aumenta a secreção de cortisol (53).

A leptina é um hormônio anoréxico derivado de adipócitos que exerce seus efeitos por meio do hipotálamo e outras regiões do cérebro, além do hipotálamo, os receptores da leptina são expressos no sistema mesolímbico (13, 57). Como a restrição energética resulta numa rápida e acentuada redução dos níveis circulantes de leptina, níveis baixos deste peptídeo podem estar associados a uma maior sensibilidade à recompensa, enquanto níveis elevados podem diminuir esta sensibilidade.

Hommel et. al. (2006) e Fulton et. al. (2006) investigaram o papel da leptina nos neurônios dopaminérgicos e ressaltaram as suas múltiplas ações no SNC, mostrando que a leptina modula a atividade dos neurônios dopaminérgicos mesolímbicos e que, ao fazê-lo, pode influenciar comportamentos relacionados aos alimentos e às drogas. Além dos efeitos da leptina sobre o apetite, vários estudos têm destacado que o consumo de alimentos palatáveis aumenta a vulnerabilidade ao uso de drogas (17-19, 50, 58, 59), reforçando nossa hipótese de que a leptina pode estar regulando o padrão de consumo de crack.

Este trabalho justifica-se pela importância da identificação de possíveis marcadores biológicos envolvidos na modulação neuroquímica do uso de crack e na necessidade de identificar o perfil e o estado nutricional destes indivíduos, para uma intervenção nutricional precoce e personalizada com embasamento científico.

# 2 **OBJETIVOS**

## 2.1 Objetivo Geral

Avaliar o estado nutricional e os níveis séricos de leptina em usuários de crack.

## 2.2 Objetivos Específicos

a) Avaliar o estado nutricional dos indivíduos por meio de parâmetros bioquímicos e antropométricos e verificar se há associação com a gravidade do uso de crack;
b) Identificar a eficácia de parâmetros antropométricos (IMC e BIA) e bioquímicos na avaliação nutricional do usuário de crack;
c) Verificar se há correlação entre níveis séricos de leptina e gravidade do uso de crack.

# 3. MÉTODOS

## 3.1 Delineamento

Estudo transversal, a coleta de dados ocorreu em até 72 horas após a baixa hospitalar.

## 3.2 Amostra

Os indivíduos deste estudo foram recrutados consecutivamente por conveniência entre abril de 2014 e abril de 2015 na Unidade de Psiquiatria de Adição do Hospital de Clínicas de Porto Alegre (HCPA). Neste período foram recrutados 108 indivíduos, destes, os primeiros 48 indivíduos com sangue coletado, foram utilizados para análise da leptina sérica. Para definição do tamanho da amostra (48 indivíduos), foi utilizado o estudo de Santolaria-Fernandez et. al.(40), que avaliou os níveis séricos de leptina em alcoolistas, por não existir na literatura estudos com usuários de crack. Para o cálculo utilizou-se o nível de significância de 5% com poder de confiabilidade de 90%, utilizando uma diferença significativa nos valores de leptina em 0,5 mcl/L. O sangue de 8 indivíduos não pôde ser analisado, por não estar adequado para realização do teste (hemólise, coagulação...), totalizando uma amostra de 40 indivíduos.

Os critérios de inclusão foram: ser do sexo masculino, usuário de crack com teste de urina positivo para cocaína no momento da admissão (teste Bioeasy® cocaína, Alere ™, Recife, Brasil); ter pelo menos 18 anos. Como critério de exclusão, os diagnósticos de demência e psicose foram pré-estabelecidos, no entanto, não houve exclusões no recrutamento.

## 3.3 Instrumentos de Coleta

Classificação Socioeconômica: Foi avaliado através do Critério de Classificação Econômica da Associação Brasileira de Empresas e Pesquisas (ABEP), este instrumento utiliza questões relativas à educação, número de eletrodomésticos, características de habitação e acesso a serviços públicos para avaliar o nível de renda e condição socioeconômica. O resumo desses indicadores classifica as populações em cinco classes: A (35-42 pontos); B (23-34 pontos); C (14-22 pontos); D (8-13 pontos); e E (0-7 pontos).

3.4 Consumo de Crack

O uso de crack foi determinado por uma entrevista padronizada, usando um questionário que incluía itens relacionados ao tipo, modo e frequência de uso.

A gravidade do uso de crack é um score estimado usando as seguintes informações: a) idade do primeiro uso; b) anos de uso e c) numero de pedras utilizadas nos últimos 30 dias, foi desenvolvido e publicado pelo nosso grupo. A idade do primeiro uso aos 11 anos de idade foi considerada como pontuação máxima: 10 pontos, com uma redução de 1 ponto por ano até os 20 anos (1 ponto) e 0, a partir dos 21 anos. Os anos de uso foram avaliados como 1 ponto por ano. O número de pedras nos últimos 30 dias foi avaliado da seguinte forma: até 5,99 = 1, 6 a 21 = 2, 22 a 40 = 3, 41 a 72 = 4, 73 a 103 = 5, 104 a 142 = 6 142 a 200 = 7, 201 a 343 = 8, 344 a 515 = 9 e 516 ou mais = 10. Os números obtidos nessas três variáveis foram adicionados para gerar um escore de gravidade do uso de crack.

3.5 Antropometria e Composição Corporal:

Foram verificados peso e estatura com a utilização da balança LD 1050 (Líder®, Brasil) com precisão de 50g com estadiômetro acoplado, para determinação do IMC (peso em kg/estatura em cm2).

A composição corporal foi analisada por meio do aparelho de bioimpedância tetrapolar Maltron BF 906 (Maltron®, Reino Unido), seguindo as instruções descritas pelo fabricante.

3.6 Instrumentos para Análise Bioquímica

Foram utilizados exames laboratoriais, que já são solicitados como rotina na Unidade de Psiquiatria de Adição do HCPA, são eles: Hemograma, Colesterol HDL, Colesterol Total, Glicose, Triglicerídeos. Para avaliação dos níveis séricos leptina**,** as amostras foram coletadas, centrifugadas e armazenadas em freezer -80$^{o}$C, localizados no Centro de Pesquisa Experimental do HCPA, para posterior análise. Os níveis séricos de leptina foram medidos, utilizando Kit comercial de acordo com as instruções do fabricante (Invitrogen, EUA), por "Enzyme Linked Immunono Sorbent Assay (ELISA)" – método baseado nas reações antígeno-anticorpo detectáveis através de reações enzimáticas.

## 3.7 Aspectos Éticos

Este estudo foi aprovado pelo Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre - Universidade Federal do Rio Grande do Sul (projeto nº 140146). Os dados foram coletados depois que cada indivíduo foi informado sobre os procedimentos e objetivos e aceitou para participar do estudo assinando o termo de consentimento livre e esclarecido (TCLE).

## 3.8 Análise Estatística

O método Kolmogorov-Smirnov (com correção de Lilliefors) foi utilizado para verificar a normalidade das variáveis. Para a análise descritiva, utilizamos media e desvio padrão ou mediana e interquartil. Os testes de Pearson e Spearman foram utilizados para correlações, e o teste de Mann-Whitney e o teste t de Student foram usados para comparar grupos. A análise estatística foi processada usando o software Statistical Package for Social Sciences (SPSS 18.0, Chicago, EUA).

## 4. ARTIGOS

## 4.1. Artigo 1: Active Brazilian crack cocaine users: nutritional, anthropometric and drug use profiles

Aceito para publicação na Revista Brasileira de Psiquiatria

Journal Abbreviation: REV BRAS PSIQUIATR
Journal ISSN: 1516-4446 2016/2017
Impact Factor: 2.049

Este artigo foi aceito para publicação conforme anexo B deste documento e aguarda publicação.

Revista Brasileira de Psiquiatria. 2018;00:000–000
Brazilian Journal of Psychiatry
Associação Brasileira de Psiquiatria
doi:10.1590/1516-4446-2017-2409

ORIGINAL ARTICLE

# Active Brazilian crack cocaine users: nutritional, anthropometric, and drug use profiles

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**Objective:** To evaluate the nutritional status of crack users and to analyze its correlation with drug use profiles.
**Methods:** Cross-sectional study with 108 crack users. Anthropometric data were assessed through body mass index (BMI) and bioimpedance (BIA) measurements. A blood test to analyze hematocrit, hemoglobin, glucose, and lipid profiles was also performed. Crack use was determined through a standardized interview.
**Results:** Based on BMI and BIA, most individuals were eutrophic (about 70%). Regarding hematological parameters, we found that hemoglobin and hematocrit levels were below normal for 32.4 and 30.6% of patients, respectively. Considering normal parameters, a large part of the sample (60.2%) had low levels of HDL cholesterol and high levels of triglycerides (38%). There were no significant correlations between drug profile and nutritional variables.
**Conclusion:** This is a pioneering study that examines the nutritional status of crack users. Our results showed that most crack users present normal anthropometric findings and the prevalence of underweight is low. However, blood analysis showed changes and a specific type of malnutrition.

**Keywords:** Crack cocaine; nutritional assessment; nutritional status; biochemical parameters

## Introduction

Crack cocaine (crack), a smoked form of cocaine, is a highly addictive and powerful stimulant that became popular in the mid-1980s and has been used worldwide ever since.[1,2] Brazil is considered the world's largest consumer of crack, with approximately 1.7 million regular users.[3,4] Recently, an epidemiological study estimated a prevalence of 0.81% of regular crack-cocaine users in Brazilian capitals, corresponding to 35% of all illicit drug users apart from marijuana.[4] Although rates of crack use are lower than those of other drugs, it has been observed that this illicit drug leads to more psychiatric hospitalizations and causes a greater demand for care.[5]

Crack use stimulates the central nervous system and activates the brain's reward systems by blocking the presynaptic reuptake of dopamine, norepinephrine, and serotonin. This increases the availability of these neurotransmitters in the synaptic cleft and causes intense feelings of pleasure.[6] Moreover, crack users often abuse other types of psychoactive substances, mostly alcohol and tobacco, which can aggravate their clinical and nutritional status.[7,8]

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Submitted Jul 13 2017, accepted Oct 07 2017.

The clinical consequences and comorbidities of crack use have been well described in a number of studies,[8-12] but there is a gap in literature regarding the nutritional profile of crack users. Malnutrition in this population may be multifactorial and could involve lower caloric intake, abnormal metabolic and gastrointestinal functions, and even deleterious drug effects.[13] Association between obesity and stimulant use (such as crack) is rare, since cocaine and amphetamines are appetite suppressants that tend to reduce body weight with their anorexic effects.[14,15]

Several studies have highlighted malnutrition and underweight in active multiple-drug users.[13,14,16-21] However, weight gain and binge eating have also been observed in people recovering from drug and alcohol dependence, which suggests the possibility that food and drugs may act on the same brain reward mechanisms.[14,22-24] Surprisingly, a pilot study conducted by our group found high rates of normal-weight and overweight crack users at hospital admission.[25] Considering that overweight is associated with multiple medical conditions, including diabetes, hypertension, and hyperlipidemia, the increased risk of morbidity and mortality could be particularly harmful when combined with the use of stimulants such as cocaine.[15,26]

This study focused on describing the previously-unknown nutritional profile of crack users, supporting early intervention based on scientific and personalized findings to aid clinical recovery. Our main hypothesis was that the severity of crack use may impair nutritional status. Due to the large number of crack users in Brazil and the increasing demand for health services, research is needed in this area.

This study aimed to evaluate the nutritional status of crack users and analyze its correlation with drug use profiles. In addition, we compared the performance of different nutritional assessment methods, such as anthropometric and biochemical parameters (blood tests).

## Methods

### *Baseline subject characteristics and study design*

A total of 108 individuals were consecutively recruited by convenience between April 2014 and April 2015 at the Serviço de Psiquiatria de Adição of the Hospital de Clínicas de Porto Alegre (HCPA), a large Brazilian teaching hospital affiliated with the Universidade Federal do Rio Grande do Sul (UFRGS) that provides free public services. All patients met the criteria for crack addiction as described by the DSM-5.[27] Crack addiction was diagnosed through a comprehensive clinical interview performed by a trained psychiatrist in charge of inpatient admissions. Inclusion criteria were: being a male crack cocaine user who screened positive for cocaine in a urine test at admission (Bioeasy® cocaine test, Alere™, Recife, Brazil); being at least 18 years old; and agreeing to provide blood samples and a signed informed consent form. Crack was required to be the drug of choice, but the use of other psychoactive substances was not an exclusion criterion. Subjects who presented symptoms compatible with dementia or psychosis or those who presented cognitive impairment that prevented comprehension of the study were excluded from the sample. These exclusion criteria were verified by a psychiatrist in a clinical interview, who used the standard recruitment center evaluation.

### *Sociodemographic characteristics and drug use profile*

The subjects' socioeconomic status was determined in accordance with the Brazilian Association of Research Companies (Associação Brasileira de Empresas e Pesquisa[28]) scale. This instrument includes questions about education, home appliances, housing characteristics, and access to public services to evaluate income level. Five classes are derived from these indicators: A (35-42 points); B (23-34 points); C (14-22 points); D (8-13 points); and E (0-7 points). Class A is the most advantaged, while class E is the poorest.

Crack use was determined through a standardized interview, using a questionnaire that included items related to the type, mode, and frequency of drug use. Severity of crack use was estimated by age of first use, years of use, and crack rocks used in the previous 30 days, as described in previous studies.[29-31] First crack use at the age of 11 was considered as 10 points, with a reduction of 1 point per year until age 20 (1 point) and 0 points for age 21 or older; 1 point was given for each year of per year crack use. The number of crack rocks used in the last 30 days was valued as follows: 1-5 = 1 point, 6-21 = 2 points, 22-40 = 3 points, 41-72 = 4 points, 73-103 = 5 points, 104-142 = 6 points, 142-200 = 7 points, 201-343 = 8 points, 344-515 = 9 points, and 516 or more = 10 points. The sum of these three variables was used to produce a crack use severity score, and the participants were categorized into a more severe or less severe group, which were divided by the median.

Daily alcohol consumption in the last 30 days was also assessed. Users mentioned the ingestion of only two types of beverage: *cachaça* (a distilled spirit made from fermented sugarcane juice, the most popular distilled alcoholic beverage in Brazil, with around 44% alcohol) and beer. For the statistical analyses, we used World Health Organization (WHO)[32] parameters, whereby 350 mL of beer or 30 mL of spirits correspond on average to 12 g of alcohol. We calculated the amount (in grams) of ethanol consumed daily. Data on the number of tobacco and marijuana cigarettes smoked in the last 30 days was also obtained in the clinical interview.

### *Anthropometry and body composition*

The anthropometric evaluation was performed within 48 hours of admission. Weight and height were verified using an LD1050 scale (Líder®, São Paulo, Brazil) with 50 g precision and with a built-in stadiometer to determine body mass index (BMI) (weight in kg/height in $m^2$). BMI was classified according to WHO cutoff points.[33] Body composition (body fat percentage) was analyzed with tetrapolar bioimpedance (BIA) (Maltron BF 906, Maltron®, Rayleigh, UK). The test was administered according to manufacturer instructions, with patients having avoided exercise in the previous 12 hours, having fasted between 2 to 3 hours, and having their last urine elimination 30 minutes prior to the test. We used American Council on Exercise parameters to classify individuals based on body fat.[34]

### *Blood tests*

Fasting blood samples were obtained for blood test analysis the morning after admission. Hematocrit and hemoglobin were analyzed with a Sysmex HST-402 (Sysmex, Hyōgo, Japan) platform that uses photometry and flow cytometry. For glucose and lipids (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides), we used the enzyme assay method in a Cobas c702 analyzer (Roche, Basel, Switzerland). We measured the hematocrit and hemoglobin levels using the reference values proposed by Hoffbrand,[35] and the glucose and lipid profiles were based on references established by the Brazilian Society of Cardiology.[36] Human immunodeficiency virus (HIV) testing was performed on all patients using the immunoblot technique with HIV-1 and HIV-2 antigens. Student's *t*-test was used to verify the difference in variables between HIV-positive and HIV-negative individuals. Since there were no significant differences between groups, all individuals were recruited for the sample.

### *Ethics*

This study was approved by the research ethics committee of the HCPA/UFRGS (project no. 140146). Data were collected after each individual was informed of the

procedures and objectives and gave permission to participate by signing an informed consent form.

*Statistical analysis*

The Kolmogorov-Smirnov method (with Lilliefors significance correction) was used to verify the normality of the variables. For the descriptive analysis, we used mean and standard deviation or median and interquartile range. The Pearson and Spearman tests were used for correlations and the Mann-Whitney *U* test and Student's *t*-test were used to compare groups. Statistical analysis was processed in SPSS version 18.0.

## Results

As shown in Table 1, we assessed the subjects' baseline characteristics. Users were mostly Caucasian and came from poor socioeconomic backgrounds. Considering their BMI and BIA, few individuals were underweight or had low body fat; most were eutrophic, overweight, or obese.

The blood tests presented in Table 2 show that the patients' hemoglobin and hematocrit levels were below normal in approximately 30% of the sample, and a large part of the sample had low levels of HDL cholesterol and high levels of triglycerides. LDL cholesterol, total cholesterol, and glucose also presented alteration, but at lower percentages. HIV prevalence was 11.1%.

Table 3 shows the participants' drug use profiles (crack, alcohol, marijuana, and/or tobacco). Crack rocks consumed per day ranged from one to 150 and the consumption period ranged from four months to 32 years. Sixty-six (61.1%) patients reported daily consumption of alcoholic beverages (*cachaça* or beer). Ethanol consumption ranged from 34.28 g to 2,000 g per day. A total of 75.9% of the subjects reported daily use of tobacco cigarettes. A total of 50 individuals (46.29% of the sample) reported marijuana consumption. Among marijuana users, consumption ranged from one to 15 cigarettes per day. As a means of evaluating the influence of ethanol on crack consumption, a Mann-Whitney *U* test was used to assess the difference between drinkers (n=66) and non-drinkers (n=42). The difference between groups was significant ($p = 0.040$), demonstrating that individuals who consumed alcohol used crack less.

There were no significant correlations between crack consumption and anthropometric measures/blood tests. The main correlations are presented in Table 4. We found positive correlations between BMI, BIA, triglycerides, cholesterol, and glucose.

Using the median crack use severity, we divided the sample of users into two groups ($\leqslant 19$ and $> 19$). There was no significant difference in the nutritional, biochemical, or drug use variables analyzed between the groups (data not shown).

**Table 1** Sociodemographic and nutritional baseline characteristics of crack users (n=108)

| Variables | Reference value | n (%) |
|---|---|---|
| Age, mean (SD) | - | 34.51 (9.22) |
| Race/ethnicity | | |
| Caucasian | - | 80 (74.1) |
| Black | - | 28 (25.9) |
| Socioeconomic class | | |
| A/B | - | 0 (0.0) |
| C | - | 5 (4.6) |
| D/E | - | 103 (95.4) |
| BMI (kg/m$^2$) | | |
| Underweight | $< 18.5$ | 6 (5.6) |
| Normal | 18.5-24.9 | 69 (63.9) |
| Overweight + obese | $> 25.0$ | 33 (30.6) |
| BIA (body fat %) | | |
| Essential fat | $\leqslant 5.0$ | 4 (3.7) |
| Average/normal | 6.0-24.0 | 84 (77.8) |
| Obese | $\geqslant 25.0$ | 20 (18.5) |

Data presented as n (%), unless otherwise specified.
BIA = tetrapolar bioimpedance; BMI = body mass index; SD = standard deviation.
BMI was classified according to World Health Organization cutoff points.[33] The subjects' body fat was classified according to American Council on Exercise parameters.[34]

## Discussion

This study provides new insights into the nutritional assessment of drug addicts. Regarding anthropometric parameters (BMI and BIA), few individuals presented low weight

**Table 2** Assessment of nutritional parameters using blood tests (n=108)

| Variables/reference value | n (%) | Mean (SD) |
|---|---|---|
| Hematocrit (%) | | 41.4 (3.6) |
| 40.0-52.0 | 75 (69.4) | |
| $< 40.0$ | 33 (30.6) | |
| Hemoglobin (mg/dL) | | 14.0 (1.2) |
| 13.5-17.5 | 73 (67.6) | |
| $< 13.5$ | 35 (32.4) | |
| Total cholesterol (mg/dL) | | 151.2 (36.5) |
| $\leqslant 200.0$ | 98 (91.6) | |
| $> 200.0$ | 9 (8.4) | |
| HDL cholesterol (mg/dL) | | 42.2 (14.1) |
| $> 40.0$ | 43 (39.8) | |
| $\leqslant 40.0$ | 65 (60.2) | |
| LDL cholesterol (mg/dL) | | 85.9 (29.5) |
| $< 129.0$ | 101 (93.5) | |
| $\geqslant 129.0$ | 7 (6.5) | |
| Triglycerides (mg/dL) | | 120.1 (63.1) |
| $< 150.0$ | 67 (62.0) | |
| $\geqslant 150.0$ | 41 (38.0) | |
| Glucose (mg/dL) | | 94.4 (34.6) |
| $< 100.0$ | 95 (88.0) | |
| $\geqslant 100.0$ | 13 (12.0) | |
| HIV | | |
| Negative | 96 (88.9) | |
| Positive | 12 (11.1) | |

HIV = human immunodeficiency virus; SD = standard deviation.
Hematocrit and hemoglobin levels were measured using the reference values proposed by Hoffbrand[35]; glucose and lipid profiles were based on references established by the Brazilian Society of Cardiology.[36]

**Table 3** Distribution of variables associated with the sample's drug use profile (n=108)

| Variables | Mean (SD) | Median (IR) |
|---|---|---|
| Years of crack use | 10.40 (7.01) | 9.0 (5.0-14.0) |
| Crack rocks used (per day) | 16.27 (23.90) | 8.0 (4.0-15.5) |
| Age of first crack use | 24.10 (8.70) | 22.0 (17.0 30.8) |
| Severity of crack use | 19.90 (8.20) | 18.5 (14.0-25.0) |
| Associated drugs (alcohol and tobacco), n (%) | | |
| Only crack | 5 (4.63) | - |
| Crack + tobacco | 17 (15.74) | - |
| Crack + tobacco + alcohol | 26 (24.07) | - |
| Crack + tobacco + marijuana | 16 (14.81) | - |
| Crack + tobacco + alcohol + marijuana | 23 (21.30) | - |
| Crack + alcohol | 10 (9.26) | - |
| Crack + alcohol + marijuana | 7 (6.48) | - |
| Crack + marijuana | 4 (3.70) | - |
| Ethanol (g/day) (n=66) | - | 400.0 (154.3-800.0) |
| Comparison of crack use between groups (rocks/day)* | | |
| With ethanol (n=66) | - | 7.0 (3.0-10.0) |
| Without ethanol (n=42) | - | 10.0 (6.0-20.0) |

IR = interquartile range; SD = standard deviation.
* Mann-Whitney *U* test, p = 0.040.

**Table 4** Correlations between body mass index, bioimpedance, and blood nutritional parameters (n=108)

| | BIA | Hematocrit | Hemoglobin | TC | HDL | LDL | Glucose | Triglycerides | Ethanol (g/day) | Tobacco cigarettes/ day | Severity crack use |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BMI* | **0.879** (> **0.001**) | -0.019 (0.844) | 0.043 (0.659) | **0.278** (**0.004**) | -0.058 (0.548) | **0.194** (**0.044**) | 0.171 (0.077) | **0.414** (> **0.001**) | 0.094 (0.336) | -0.054 (0.576) | -0.023 (0.814) |
| BIA* | 1 | -0.053 (0.587) | 0.020 (0.834) | **0.302** (**0.001**) | -0.035 (0.719) | **0.220** (**0.022**) | **0.224** (**0.020**) | **0.380** (> **0.001**) | 0.086 (0.373) | -0.052 (0.596) | 0.058 (0.549) |
| Hematocrit* | | 1 | **0.932** (> **0.001**) | 0.007 (0.942) | -0.186 (0.055) | 0.025 (0.798) | -0.144 (0.137) | 0.181 (0.061) | -0.102 (0.293) | 0.167 (0.084) | -0.176 (0.068) |
| Hemoglobin* | | | 1 | 0.052 (0.596) | -0.184 (0.056) | 0.021 (0.830) | -0.095 (0.330) | **0.263** (**0.006**) | -0.071 (0.465) | 0.155 (0.108) | -0.152 (0.116) |
| TC† | | | | 1 | **0.403** (> **0.001**) | **0.832** (> **0.001**) | 0.163 (0.091) | **0.399** (< **0.001**) | 0.142 (0.142) | 0.031 (0.753) | 0.001 (0.991) |
| HDL† | | | | | 1 | 0.146 (0.131) | 0.094 (0.334) | **-0.341** (< **0.001**) | **0.326** (**0.001**) | -0.120 (0.217) | -0.089 (0.362) |
| LDL† | | | | | | 1 | 0.080 (0.411) | **0.213** (**0.027**) | -0.078 (0.422) | 0.116 (0.230) | -0.004 (0.964) |
| Glucose† | | | | | | | 1 | 0.183 (0.059) | 0.064 (0.510) | -0.052 (0.590) | 0.047 (0.627) |
| Triglycerides† | | | | | | | | 1 | 0.044 (0.649) | 0.043 (0.657) | 0.023 (0.813) |
| Ethanol (g/day)† | | | | | | | | | 1 | -0.064 (0.512) | 0.016 (0.871) |
| Tobacco cigarettes/day† | | | | | | | | | | 1 | -0.026 (0.786) |
| Severity crack use† | | | | | | | | | | | 1 |

TC = total cholesterol.
Values in bold represent correlations coefficients (r) with $p < 0.05$.
* Variable with normal distribution.
† Variable with asymmetric distribution.

and body fat, with most being normal weight, overweight, or obese. Although a number of studies have reported malnutrition and underweight in drug users,[13,14,16-21] our study found a low prevalence. Nevertheless, this does not exclude other specific deficiencies. The blood work revealed important alterations in a significant proportion of our sample, such as low levels of hemoglobin and hematocrit, which can be associated with protein-energy malnutrition and anemia. However, we found no significant correlations between crack use variables and any of the nutritional parameters we evaluated.

In one of the first studies on nutrition in drug addicts, Santolaria-Fernández et al.[16] demonstrated that 90% of drug users suffer from protein-energy malnutrition. Underweight (BMI < 18.5 kg/m$^2$) has already been demonstrated in multidrug users (60% prevalence)[18] and injection drug users (50% prevalence).[20] Despite this, we found no prevalence of low weight. One important bias is that the other studies involved multiple-drug users

from other locations with different drug profiles, usage types and frequency, while ours included only crack cocaine users with associated alcohol and tobacco consumption. Since this is the first study to ever sample such a profile, we cannot compare it confidently with studies covering different types of drug users.

There are data on overweight and obesity in recovering drug users, but not in current drug users.[14,22-24] For example, Cowan & Devine[14] studied drug addicts at different stages of recovery and reported that most have poor diets during active addiction, are generally undernourished at the beginning of treatment, and become overweight and obese during recovery. During abstinence, they may seek alternative ways of activating the brain reward system and the inhibition of dopamine reuptake, with one common outlet being overeating.[37] To reinforce this hypothesis, Ersche et al.[38] reported that cocaine-dependent men had a higher food intake than non-users, specifically foods high in fat and carbohydrates, but had no concomitant increase in body weight. The authors suggest that this is due to cocaine's interference with normal metabolic processes, resulting in an imbalance between fat intake and storage.

Regarding hematological parameters, we found that hemoglobin and hematocrit levels were below normal in 32.4% and 30.6% of patients, respectively. These decreased levels may indicate protein-energy malnutrition and anemia. In these cases, anemia may be associated with a diet poor in micronutrients, especially iron, as well as insufficient protein intake and clinical problems (decreased hydrochloric acidproduction, decreased intrinsic factor secretion, intestinal perforations, bacterial or infectious diseases).[39] Supporting our findings that BMI alone is a poor indicator of nutritional status, Nazrul et al.[18] demonstrated that 74% of drug addicts showed clinical signs of nutrient deficiency, with significantly lower hemoglobin and total serum protein levels. Meanwhile, Ross et al.[19] found blood markers indicating that 50% of all subjects had iron or vitamin deficiencies.

Compared to normal parameters, a large proportion of our sample (60.2%) had low levels of HDL cholesterol and high levels of triglycerides (38%). LDL cholesterol (6.5%), total cholesterol (8.4%), and glucose (12%) also presented alteration, but at lower percentages. This can probably be ascribed to the subject's low quality of life, lack of access to healthy food and physical activity, and high alcohol consumption. Tang et al.[20] studied HIV-positive and HIV-negative drug addicts and identified other aspects of nutritional deficiencies, such as food insecurity and low levels of caloric and protein intake. Our study also found low levels of HDL, which may be associated with a lack of social, economic, and physical activities. In a study on specific deficiencies in multiple-drug users, Nazrul Islam et al.[17] found lower concentrations of antioxidant vitamins E, C, and A in this population, suggesting a lack of access to certain foods. The damage and consequences of crack use can lead to numerous specific nutritional deficiencies and may require further investigation.

We found positive correlations between BMI, BIA, triglycerides, cholesterol, and glucose, which reinforces that body fat is associated with high serum lipid levels and glucose alterations. Changes in lipid and glucose profiles, alcohol consumption, and smoking are risk factors for the development of chronic diseases such as diabetes, dyslipidemias, hypertension, and metabolic syndrome. Considering that these individuals are at risk for cardiovascular problems due to drug use, the sum of these factors may increase the probability of disease and malnutrition.

There was no significant correlation between severity of crack use and anthropometric or biochemical variables. However, individuals who consumed alcohol used crack less ($p < 0.05$), suggesting a compensatory behavior involving ethanol. Crack use has been reported to induce intestinal perforations, gastric ulcerations, retroperitoneal fibrosis, abdominal pain, nausea, mesenteric ischemia, and esophagitis, thus impairing absorption, digestion, and metabolism[9] and leading to malnourishment. As for cardiovascular consequences, cocaine can cause increased heart rate and blood pressure, endothelial dysfunction, arrhythmia, and atherosclerosis. Combining cocaine with other substances (such as alcohol, marijuana, and/or tobacco) and other risk factors, such as overweight and obesity, can cause cumulative health damage.[26,40]

The high level of alcohol consumption (61%) among crack users was an unexpected finding. They reported consuming it in large quantities, mainly in the form of *cachaça*, exceeding the maximum daily amount of ethanol (30 g) recommended by the WHO.[32] Our results show high alcohol consumption, indicating that this factor should also be a concern in the treatment of crack addiction. The combined use of cocaine/crack and alcohol induces the biotransformation of cocaine, leading to the transesterification of a metabolite, which results in a substance known as cocaethylene. This increases the duration of euphoric effects and is more cardiotoxic than consuming each drug separately.[7] We also observed a high prevalence of tobacco and marijuana use, with 75.9% and 46.29% of the individuals involved in this behavior, respectively. It has been well documented that smoking can cause numerous diseases, such as cancer, emphysema, and cardiovascular diseases. The nutritional effects of smoking include an increase in free radicals and a decrease in antioxidants.[41] Although crack is much more deleterious than tobacco or marijuana, the effects of chronic associated use can be compounded.

We found that users from classes D and E were mostly Caucasian, characterizing a low-income population with little access to education. HIV prevalence in this group is high (11.1%) compared to the general population, confirming that crack users tend to engage in high-risk behaviors.[8,42] These social and clinical factors, when associated with crack use, can cause even further damage to their nutritional status. Since crack use is associated with complex social issues,[43] these individuals could benefit from lifestyle intervention programs, which have had positive results in the obese, diabetics, and binge eaters.[44-47]

Among the present study's limitations is the fact that we did not evaluate the impact of alcohol and marijuana consumption on nutritional status, and our sample consisted exclusively of male subjects. Moreover, we did not evaluate control subjects, which would have been important

for comparison with the crack group. We also evaluated subjects seeking inpatient treatment who, therefore, do not represent the general population of crack-cocaine users. However, the present study's pioneering results could serve to guide further research on the matter. In fact, we are already developing a case-control trial protocol to better elucidate the nutritional profile of crack users and evaluate the influence of nutritional aspects on treatment prognosis.

In summary, this was a pioneering study that examined the nutritional status of crack users. The BMI of most of them was within the normal, overweight, or obese range. However, their blood tests indicated alterations in hematocrit and hemoglobin levels and in glucose and lipid profiles. This shows that, although crack users are not necessarily underweight, they present other specific nutritional deficiencies that qualify them for a diagnosis of malnutrition. Furthermore, their condition may be associated with other issues that deserve attention, such as alcohol consumption and social problems. This study is the first step towards highlighting the importance of nutrition in the treatment of drug addiction for this marginalized population. We intend to follow these users and evaluate their changes in nutritional status during recovery, as well as food intake and food-related preferences during this period.

## Acknowledgements

We thank all participants for collaborating in the present study, the HCPA professionals for assisting in blood collection and biochemical analysis, and the Fundo de Incentivo à Pesquisa e Eventos (FIPE) – HCPA, for providing funding for this research.

## Disclosure

The authors report no conflicts of interest.

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2. Artigo 2: Leptin levels are inversely correlated with severity of crack-cocaine use: A preliminary study

Revista escolhida para submissão: *Neuroscience Letters*

2016 Impact Factor: 2.18

# Leptin levels are inversely correlated with severity of crack-cocaine use: A preliminary study

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## HIGHLIGHTS

• Drug use and appetite share the same brain reward processes;
• Leptin may be modulating crack cocaine use;
• Leptin can be used as a biomarker for drug use.

ABSTRACT

Background: Crack-cocaine is an important public health problem in Brazil and worldwide. It is a potent form of cocaine which results in rapid and damaging stimulating effects on the central nervous system through inhibition of the dopamine transporter. Some studies have suggested that both food and drugs - including crack, can act on the same brain reward mechanisms, altering the dopamine pathways that modulate behavioral responses. Our hypothesis was that leptin, a well-known peptide that modulates energy metabolism and appetite, can be used as a biomarker for drug use. Methods: Anthropometric data, drug use profiles, and leptin serum levels were evaluated in a cross-sectional study of 40 crack-cocaine users. Results: Leptin showed an inverse correlation with the severity of crack use, and this correlation remained when corrected by body mass index (BMI) and body composition by bioimpedance (BIA). The majority of subjects were eutrophic or overweight/obese considering BMI and BIA, and these variables were not significantly associated with the

severity of crack use, but positively correlated with leptin levels. Conclusions: Our preliminary findings suggest that leptin could be involved in drug use severity, perhaps through pathways similar to those whereby it modulates food intake. Considering the anthropometric parameters, these findings provide additional evidence that low weight is not predominant in crack users.

Keywords: Crack cocaine. Leptin. Biomarkers. Drug severity. Brain reward system

## 1. Introduction

Crack-cocaine (Crack) addiction is an important public health problem in Brazil and worldwide. Crack is a potent smoked form of cocaine, which results in rapid and damaging stimulating effects on the central nervous system through inhibition of the dopamine transporter, leading to a significant increase in extracellular mesolimbic dopamine [13]. Identification of biomarkers may be useful in untangling neurobiological processes involved in drug abuse for both clinical and research purposes [19].

Jeynes and Gibson [8], in a recent narrative review assessing the relationship between substance use disorders and nutrition, noted the demand for detailed nutritional assessment to determine specific micronutrient needs, and found evidence of overlaps in brain chemical reward signaling between drug addictions and eating, suggesting a link between food restriction, satiety signaling, and substance abuse. Malnutrition in this population may be multifactorial, and the drug itself may act as an appetite suppressant, reducing body weight with its anorexic effects. On the other hand, weight gain and binge eating have been observed in recovering addicts [3, 18]. Surprisingly, a pilot study conducted by our group showed high rates of crack users with normal weight and overweight at hospital admission [24].

Volkow et al. [20] suggested the possibility that food and drugs, such as crack, may act on the aforementioned brain reward mechanisms (i.e., disruption of dopamine pathways that modulate behavioral responses). Therefore, it is not surprising that neurotransmitters implicated in food intake would also be implicated in drug-seeking behaviors. In this line of though, peptides that regulate food intake—such as leptin—could also influence drug-reinforcing effects. Leptin is an adipocyte-derived anorexic hormone that exerts its effects via the hypothalamus and other brain regions, including the reward system [14, 15]. Within this context, our hypothesis is that neuroendocrine pathways involved in appetite may also be involved in the neurobiological processes that regulate crack consumption. There are no studies in the literature indicating an association between crack and leptin. The main objective

of this study was to investigate the correlation between serum concentrations of leptin and the severity of crack use. As a secondary objective, we evaluated possible correlations between the severity of crack use and anthropometric parameters.

## 2. Methods

### 2.1 Baseline subject characteristics, study design and variable definition

Forty individuals were recruited from the Addiction Psychiatry Unit of Hospital de Clínicas de Porto Alegre (HCPA), a large teaching hospital affiliated with the Federal University of Rio Grande do Sul, Brazil. Inclusion criteria were: being a male crack user with a positive urine screening test for cocaine (Bioeasy® cocaine test, Alere™, Recife, Brazil) at admission; being at least 18 years old, and agreeing to provide blood samples and a signed informed consent form. Subjects who were considered clinically unable to participate (e.g., in cases of tuberculosis, psychosis, dementia, or mental retardation) were excluded from the sample. These exclusion criteria were verified by a psychiatrist in a clinical interview, using the standard evaluation of the recruitment center.

Crack use was assessed by a standardized interview, using a questionnaire that included items related to the type, mode, and frequency of drug use. Severity of crack use was estimated using age at first crack use, years of crack use, and crack rocks smoked in the previous 30 days, as in previous studies of our group [12, 17, 22]. First crack use at age 11 years was assigned the maximum score of 10 points, from which 1 point was deducted per additional year of patient age at first use until age 20 (1 point); first use at age 21 or older was assigned zero points. Duration of crack use was scored using a simple system of 1 point per year. The number of crack rocks smoked in the last 30 days was scored as follows: 0–5.99=1, 6–21=2, 22–40=3, 41–72=4, 73–103=5, 104–142=6, 142–200=7, 201–343=8, 344–515=9, and ≥516=10. Finally, these three parameter scores were added to generate an overall score of crack use severity. Users were then categorized into two groups (more vs. less severe crack use) according to the median overall score.

### 2.2 Anthropometric evaluation and body composition

Anthropometric evaluation was performed within 48 hours of admission. The body mass index (BMI) was calculated using the height and weight of each participant and classified according to the World Health Organization cutoff points [10]. Body composition (fat percentage) was analyzed by tetrapolar bioimpedance analysis (BIA) using a Maltron BF 906® device (Maltron, UK), following pre-test instructions described by the manufacturer.

We used the American Council on Exercise parameters to classify individuals by body fat percentage [2].

2.3 Blood tests

A blood sample was collected during the first 24 h of hospitalization, after 10h of fasting. Serum leptin levels were measured by sandwich-ELISA using a commercial kit, in accordance with the manufacturer's instructions (Invitrogen, USA). In short, samples were added to the appropriate microtiter wells and biotinylated anti-human leptin (biotin conjugate) solution was pipetted into each well (except for the chromogen blanks). The plate was covered and incubated for 2 hours at room temperature. Plate wells were later washed four times and streptavidin-horseradish peroxidase working solution was added to each well (except for the chromogen blanks) and incubated for 30 minutes at room temperature. After washing, stabilized chromogen was added to each well and the plate was incubated for 30 minutes at room temperature in the dark. After addition of stop solution, leptin was quantitated (absorbance set at 450 nm). The standard curve (ranging from 0 to 1,000 ng/mL) demonstrated a direct relation between optical density and leptin concentration.

2.4 Ethics

The study was approved by the Hospital de Clinicas de Porto Alegre Research Ethics Committee (project number 140146). Before data collection, all participants were informed of the procedures and objectives of the study and provided written informed consent for participation.

2.5 Statistical analysis

The Kolmogorov-Smirnov method (with Lilliefors significance correction) was used to test for normality of distribution. For descriptive analysis, we calculated means and standard deviations or medians and interquartile ranges as appropriate. Pearson and Spearman tests were used to calculate correlations, and the Mann-Whitney U and Student's t tests were used to compare groups. Leptin levels were corrected by BMI and BIA. Statistical analyses were processed in PASW Statistics 18.0 (SPSS, Inc., Chicago, USA).

3. Results

3.1 Demographic and drug-use characteristics stratified by severity of crack use

Considering their BMI and BIA findings, few individuals were underweight (5%) or had low body fat (2.5%). Most had normal weight (65%) or overweight/obesity (30%). The group with less crack severity had higher levels of leptin and BMI. Table 1 lists the subjects' demographic, anthropometric and drug-use characteristics stratified by severity of crack use.

"PLEASE INCLUDE TABLE 1 ABOUT HERE"

3.2 Severity of crack use and Correlations

The severity of crack use showed an inverse correlation with leptin. After correcting leptin by BMI and BIA, the association with severity of use remained. BMI and BIA demonstrated no significance with severity of crack use, however; they showed a tendency to an inverse correlation ($p = 0.07$), and were positively correlated with leptin (Table 2).

"PLEASE INCLUDE TABLE 2 ABOUT HERE"

4. Discussion and conclusions

The main finding of this study was that serum leptin showed an inverse correlation with the severity of crack use, and this correlation remained when corrected for BMI and BIA. When comparing the groups by severity of crack use, we also found that the group with more severe had lower serum levels of leptin. It is possible that, in addition to appetite, leptin may be modulating crack consumption. This is a pioneering study; there are no studies on leptin and crack, only some research, in other models, with cocaine.

In an animal protocol, Hommel et. al. [7] and Fulton et. al.[6], investigated the role of leptin in dopaminergic neurons and the multiple actions of leptin in the central nervous system, showing that leptin modulates the activity of mesolimbic dopaminergic neurons and may influence food and drug-related behaviors. In a study with rats, You et. al.[25], demonstrated that cocaine use decreased plasma levels of leptin, and revealed reciprocal antagonistic effects between cocaine and leptin. Shen et. al.[14], also using animal models, showed that leptin signaling is a negative regulator of the effect of addictive drugs and might also are involved in mediating the inhibitory effect of natural reward upon drug reward.

In previous human clinical studies, Ersche et. al.[5],found lower serum levels of leptin in cocaine users when compared to non-users, with cocaine-dependent users reporting higher food intake (specifically, of foods rich in fats and carbohydrates), but presenting no

concomitant increase in body weight. The authors suggested that the sympathetic effects of cocaine may inhibit leptin production and facilitate overeating. This imbalance during active use can lead to excess weight gain when cocaine use is discontinued during recovery. In contrast, Bouhlal et. al. [1], in the first clinical study on this topic with controlled drug administration, assessed serum concentrations of appetitive hormones after an acute cocaine administration (25 mg intravenously) and found no subsequent effect on leptin or ghrelin levels. In addition to the effects of leptin on appetite, several studies have highlighted that consumption of palatable food increases vulnerability to drug use [4, 9, 16, 20, 21, 23], reinforcing our hypothesis that leptin may regulate crack-related behavior.

Considering the anthropometric parameters measured here (BMI and BIA), few individuals presented low body weight or low percentage of body fat. Most are within the normal weight, overweight or obesity range; these findings provide additional evidence that low weight is not predominant in crack users. However, they may present other specific nutritional deficiencies that qualify them for a malnutrition diagnosis, and these should be investigated. When analyzing the severity of crack use, BMI and BIA demonstrated no significant associations with severity of crack use; however, they showed a tendency to an inverse correlation ($p = 0.07$). The group with the greatest severity showed a lower BMI. A possible explanation for lower body mass in individuals with higher severity can be the anorexic effect of crack, as well as the damage to the metabolic and gastrointestinal functions caused by the drug per se [11]. Our hypothesis is that in addition to the deleterious physiological effects of crack in the body, leptin may be a protective factor and low serum levels of this peptide increase drug consumption. It should be noted that many factors contribute to weight loss vulnerability, including social, economic, neurochemical and dietary conditions, suggesting that further controlled studies will be needed to confirm this idea.

It is important to consider that this study has some limitations, such as the absence of a control group and the sample size (preventing more robust statistical analyses); however, this was a preliminary study, and we intend to conduct more controlled research in order to overcome some of these limitations. Our findings suggest that leptin could be involved in drug-use severity, perhaps through pathways similar to those whereby it modulates food intake; considering the anthropometric parameters, these findings provide additional evidence that low weight is not predominant in crack users.

Acknowledgments

We thank all participants for cooperating with the present study, the HCPA staff for assisting in blood collection and biochemical analysis, and the HCPA Research and Event Incentive Fund (Fundo de Incentivo à Pesquisa e Eventos, FIPE-HCPA) for providing funding for this research.

Conflicts of interest, source of funding and authorship

The authors have no conflicts of interest to declare. All authors made an active contribution to the drafting of the manuscript and all of them critically reviewed its content and approved the final version submitted for publication. Funding for this study was provided by the HCPA Research and Event Incentive Fund (Fundo de Incentivo à Pesquisa e Eventos, FIPE-HCPA).

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Table 1. Demographic and drug-use characteristics stratified by severity of crack (n = 40)

| | Total | Severity of crack use score | | p |
|---|---|---|---|---|
| | | Less ≤17 (n=21) | More >17 (n=19) | |
| Age, mean (SD) | 33.23 (7.9) | 33.00 (8.4) | 33.47 (7.6) | 0.853 |
| Ethnicity, | | | | |
| Caucasian, n (%) | 26 (65%) | 15 (71.4) | 11 (57.9) | 0.573 |
| Black, n (%) | 14 (35%) | 4 (28.6) | 8 (42.1) | |
| BMI (kg/m$^2$), mean (SD) | 23.54 (3.4) | 24.70 (3.1) | 22.26 (3.3) | **0.021** |
| Underweight, n (%) | 2 (5.0) | 0 (0.00) | 2 (10.5) | 0.226 |
| Normal weight, n (%) | 26 (65.0) | 13 (61.9) | 13 (68.4) | |
| Overweight/obese, n (%) | 12 (30.0) | 8 (38.1) | 4 (21.1) | |
| BIA, mean (SD) | 18.30 (6.6) | 20.17 (5.6) | 16.23 (7.1) | 0.057 |
| Essential fat, n (%) | 1 (2.5) | 0.00 (0.00) | 1 (5.3) | 0.695 |
| Average/normal, n (%) | 31 (77.5) | 16.00 (76) | 15 (78.9) | |
| Obese, n (%) | 8 (20) | 5.00 (24) | 3 (15.8) | |
| Leptin (ng/ml), median [IQR] | 9 [2; 10] | 10 [6; 11] | 4 [1; 10] | **0.014** |
| Leptin/BMI | 0.35 [0.08; 0.4] | 0.40 [0.21; 0.4] | 0.25 [0.03; 0.4] | **0.027** |
| Leptin/BIA | 0.39 [0.17; 0.5] | 0.42 [0.28; 0.5] | 0.32 [0.06;0.4] | **0.036** |

BMI, body mass index; BIA, tetrapolar bioimpedance analysis. BMI was classified according to World Health Organization cutoff points. Body fat was classified according to American Council on Exercise parameters.

Table 2 – Severity of crack use and Correlations

| | BMI | BIA | Leptin (ng/ml) | Severity of crack use |
|---|---|---|---|---|
| BMI | - | 0.912 (<0.001[1]) | 0.687 (<0.001[1]) | -0.283 (0.077[2]) |
| BIA | | - | 0.740 (<0.001[1]) | -0.188 (0.244[2]) |
| Leptin (ng/ml) | | | - | -0.351 (0.026[1]) |
| Leptin/BMI | | | | -0.323 (0.042[1]) |
| Leptin/BIA | | | | -0.322 (0.043[1]) |
| Severity of crack use | | | | - |

[1]Spearman correlation coefficient.

[2]Pearson correlation coefficient.

# 4 CONCLUSÕES E CONSIDERAÇÕES FINAIS

Este estudo é pioneiro na forma de avaliação do estado nutricional por métodos antropométricos e bioquímicos e níveis séricos de leptina em usuários de crack. De acordo com as revisões feitas, esta é a primeira vez que estes dados são descritos na literatura. Conforme nossos achados demonstram, a desnutrição em função da massa corporal não foi identificada em nossos pacientes. Em nosso estudo, grande parte dos usuários (63,9%) apresentou um IMC dentro dos parâmetros de normalidade, sendo encontrados, inclusive, indivíduos com sobrepeso e obesidade (30,6%). Considerando que o uso de crack é um potente fator de risco para doenças cardiovasculares (60), o sobrepeso e a obesidade, a dislipidemia e outras alterações metabólicas decorrentes da má alimentação, podem intensificar estes riscos e comprometer a saúde. No entanto, mesmo apresentando um IMC dentro da normalidade ou excesso de peso, isto não significa que estes usuários não possuam outras carências em relação à ingestão de alimentos. Os parâmetros bioquímicos indicaram alterações nos níveis de hematócrito e hemoglobina e nos perfis de glicose e lipídios. Isso mostra que, embora os usuários de crack estejam classificados como eutróficos pelo IMC, estes podem apresentar outras deficiências nutricionais específicas.

O IMC *per se* não descreve a composição corporal e deficiências nutricionais séricas; o método mostra algumas limitações e não pode ser utilizado como instrumento único de avaliação nutricional. A BIA (que avalia a composição corporal) e os exames bioquímicos devem ser incluídos na avaliação do estado nutricional do usuário de crack para maior precisão no diagnóstico. É importante salientar que o estado nutricional pode estar relacionado a outras questões que merecem atenção, como o consumo associado de outras drogas (maconha, tabaco, álcool etc..), à vulnerabilidade social e questões neuroquímicas (que envolvem o apetite e a ingestão de alimentos)(30, 31, 41).

Volkow et. al. (50), sugerem a possibilidade de que alimentos e drogas, como o crack, possam estar atuando pelos mesmos mecanismos de recompensa do cérebro. Assim, não é surpreendente que os neurotransmissores e peptídeos que regulam a ingestão de alimentos - como a leptina - também possam estar influenciando os efeitos gratificantes do crack. Um achado importante e inédito em nosso estudo preliminar com 40 pacientes foi a correlação negativa da gravidade do uso de crack com os níveis séricos de leptina, sinalizando possivelmente um efeito “protetor” da leptina para o uso de SPA, demonstrando que as vias

neuroendócrinas envolvidas no apetite também podem estar envolvidas nos processos neurobiológicos que regulam o consumo de crack. Além dos efeitos da leptina sobre o apetite, vários estudos têm destacado que o consumo de alimentos hiperpalatáveis aumenta a vulnerabilidade ao uso de drogas (17-19, 50, 58, 59), reforçando a nossa hipótese de que a leptina pode regular o comportamento relacionado à cocaína.

A descoberta de novos biomarcadores pode ser útil na identificação de processos neurobiológicos envolvidos no abuso de drogas, tanto para fins clínicos quanto de pesquisa. Como perspectiva, temos o interesse de dar continuidade a este estudo por meio do desenvolvimento de uma linha de pesquisa neste tema (Comportamento alimentar e adição), com estudos caso-controle e ensaios clínicos para investigar as possíveis correlações da leptina por métodos mais controlados. Outra proposta está em analisar mais variáveis (possíveis biomarcadores) como grelina, GLP-1 e insulina, bem como avaliar questões de comportamento/transtornos alimentares e carências nutricionais específicas (micronutrientes) nesta população.

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**ANEXOS**

Anexo A: Termo de Consentimento Livre Esclarecido (TCLE)

Você está sendo convidado a participar da pesquisa **"ASSOCIAÇÃO ENTRE ESTADO NUTRICIONAL, NÍVEIS SÉRICOS DE LEPTINA E PADRÃO DE CONSUMO DE *CRACK",*** realizada pelo Centro de Pesquisa em Álcool e Drogas (CPAD) da Universidade Federal do Rio Grande do Sul (UFRGS) tendo como responsável o Prof. Dr. Flávio Pechansky. Esta pesquisa tem como objetivo principal buscar uma relação entre o seu estado nutricional e o seu comportamento com relação ao uso de substâncias e sua alimentação. Para isto serão realizadas avaliações nutricionais durante o período de internação hospitalar. Você irá fazer uma coleta de sangue em jejum de 12 horas realizada através da veia do braço, o que pode causar um pequeno desconforto pela picada da agulha. O material utilizado é descartável, portanto, com pouco risco de transmissão de doenças. Você também será convidado a responder um questionário sobre seu hábito e comportamento alimentar. Você poderá sentir algum desconforto em discutir estes aspectos durante as avaliações. Você pode solicitar a qualquer momento a interrupção dos procedimentos e das avaliações, sem necessidade de fornecer explicações e sem qualquer prejuízo ao seu tratamento.

Todos os dados pessoais serão confidenciais. Os resultados do estudo poderão ser publicados em revista científica ou discutidos com profissionais da saúde de maneira coletiva, sem citar seu nome, ou qualquer outra forma que possibilite a sua identificação.

A sua participação é voluntária. Você só participará se quiser e a sua participação não implicará em qualquer tipo de remuneração. Você pode decidir não participar mais em qualquer momento deste estudo, sem precisar justificar e sem que isto prejudique qualquer forma de tratamento que lhe é oferecido.

Você poderá solicitar novos esclarecimentos ou tirar suas dúvidas ligando para o CPAD (51 33596472) ou para o Comitê de Ética em Pesquisa do HCPA que aprovou este projeto (51 33598304), que funciona de segunda à sexta das 8 às 17 horas.

A assinatura do Termo de Consentimento Informado será efetuada em duas vias, permanecendo uma delas com você e outra com o CPAD.

Declaro que fui informado dos objetivos e de como vou participar deste estudo de forma clara, e que as minhas dúvidas foram respondidas.

Porto Alegre, _____de_____, de 20____.

Nome do Pesquisador: _____

Assinatura do Pesquisador: _____

Nome do Participante:_____

Assinatura do Participante: _____

**Anexo B**: Carta de aceite artigo 1

Brazilian crack cocaine active users: nutritional, anthropometric and drug use profiles

Revista Brasileira de Psiquiatria - Decision on Manuscript ID RBP-2017-OA-2409.R1

07-Oct-2017

Dear Mrs. Escobar:

We have completed our review of your manuscript "Brazilian crack cocaine active users: nutritional, anthropometric and drug use profiles" and are pleased to accept it for publication in Revista Brasileira de Psiquiatria. The comments of the reviewer(s) who reviewed your manuscript are included at the foot of this letter.

Thank you for your contribution. We look forward to your continued contributions to the Journal.

Sincerely,
Prof. Rafael Freire
Editor, Revista Brasileira de Psiquiatria
rafaelcrfreire@gmail.com, marimochco@yahoo.com.br

Reviewer: 1

Comments to the Author
Os autores realizaram as modificações solicitadas e acredito que o manuscrito deva ser aceito para publicação.

Reviewer: 2

Comments to the Author
I found the search results very interesting. Brings relevant clinical information on the nutritional status of crack users. I encourage the development and continuity of the line of research proposed by the authors.

**Anexo C**: Carta de submissão artigo 2


**Submissions Being Processed for Author Mariana Escobar, PhD**

Page: 1 of 1 (1 total submissions) Display 10 results per page.

| Action | Manuscript Number | Title | Initial Date Submitted | Status Date | Current Status |
|---|---|---|---|---|---|
| Action Links | NSL-172048 | Leptin levels are inversely correlated with severity of crack-cocaine use: A preliminary study | 04 Dec 2017 | 04 Dec 2017 | With Editor |

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1 mensagem

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Dear Dr. Escobar,

Your submission entitled "Leptin levels are inversely correlated with severity of crack-cocaine use: A preliminary study" has been assigned the following manuscript number: NSL-172048.

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Thank you for submitting your work to Neuroscience Letters.

Kind regards,

Neuroscience Letters

**Anexo D**: Artigos publicados durante o período do doutorado

1. Willhelm, F. F., Escobar, M., & Perry, I. D. S. (2013). Alterações na composição corporal e em parâmetros antropométricos de dependentes de crack internados em unidade de adição. *Jornal Brasileiro de Psiquiatria. Rio de Janeiro. Vol. 62, n. 3 (jul./set. 2013), p. 183-190*.

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3. Soares, C. M., Escobar, M., Vargas, M. D. S., & Grassi, T. (2016). Transtornos alimentares em homens abstinentes de substâncias psicoativas em tratamento ambulatorial. *Clinical and biomedical research. Porto Alegre. Vol. 36, n. 4,(2016), p. 199-205*.

4. Sukop, P. H., Kessler, F. H. P., Valerio, A. G., Escobar, M., Castro, M., & Diemen, L. V. (2016). Wernicke's encephalopathy in crack–cocaine addiction. *Medical hypotheses*, *89*, 68-71.