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AVALIAÇÃO DO PERFIL LIPÍDICO SÉRICO EM PACIENTES PSIQUIÁTRICOS COM TENTATIVA DE SUICÍDIO

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Casa de Papelão
Autor: Criolo

Olhos nos olhos
Sem dar sermão
Nada na boca
E no coração
Seus amigos são
um cachimbo e um cão
Casa de papelão
Olhos nos olhos
Preste atenção
Olha a ocupação
Só ficou você
Só restou você
Ruivo louco
Sangue em choro
Pra agradar a opressão
Não de foice ou faca
Esquartejada a alma
Amarga amassa a lata
Estoura pulmão
Toda pedra acaba
Toda brisa passa
Toda morte chega e laça
São prá mais de um milhão
Prédios vão se erguer
E o glamour vai colher
Corpos na multidão
Na minha mente várias portas
E em cada porta uma comporta
Que se retrai e às vezes se desloca
E quantos segredos não foram guardados nessa maloca
Flutuar no céu poluído dessa cidade e beber
Toda sua mentira
Esperança minha, torneira sem água
Moeda? É religião que alicia
Vamos cantar pra nossos mortos
Vamos chorar pelos que ficam
Orar por melhores dias
E se humilhar por um novo abril
Não dê foice ou faca
Esquartejada a alma
Amarga amassa a lata
Estoura pulmão
Toda pedra acaba
Toda brisa passa
Toda morte chega e laça
São prá mais de um milhão
Prédios vão se erguer
E o glamour vai colher
Corpos na multidão

SUMÁRIO

RESUMO

Objetivo: O suicídio é um problema de saúde pública de alta complexidade. Muitos marcadores periféricos têm sido pesquisados para identificar o comportamento suicida. Colesterol e suas frações foram propostos como biomarcadores para esta condição. Esta pesquisa tem por objetivo analisar o perfil lipídico sérico, PCR (proteína C reativa), BDNF (fator neurtotrófico derivado de cérebro), S100B e leptina em indivíduos diagnosticados com transtorno de humor (bipolar ou depressão maior) com uma tentativa recente de suicídio e em indivíduos com o mesmo diagnóstico e sem tentativa de suicídio anterior.

Métodos: Um total de 86 indivíduos com transtorno de humor foi incluído neste estudo. Cinquenta indivíduos apresentaram um episódio de tentativa de suicídio nos últimos 15 dias e trinta e seis indivíduos não tinham histórico de tentativa de suicídio. O perfil lipídico sérico foi avaliado para Colesterol total, HDL, LDL e triglicerídeos.

Resultados: Após o ajuste para a duração da doença e do episódio atual, sexo, uso de anticonvulsivantes e SSRI (inibidor seletivo da recaptação da serotonina), o IMC (índice de massa corporal) e circunferência da cintura, encontramos IMC, circunferência de cintura e triglicerídeos séricos diminuídos em indivíduos com tentativa de suicídio quando comparados com indivíduos sem tentativa de suicídio. No entanto, não foram encontradas diferenças entre os níveis de colesterol total, LDL, HDL, leptina, BDNF, PCR e S100B entre indivíduos com e sem tentativa de suicídio.

Conclusões: Estes dados não sustentam a hipótese de que o colesterol e suas frações estão associados ao comportamento suicida em uma amostra de pacientes com transtornos de humor. Entretanto, favorecem a idéia de que a adiposidade é diferenciada em pacientes com tentativa de suicídio recente comparado aos pacientes sem tentativa de suicídio, o que sugere uma comunicação alterada tecido adiposo-sistema nervoso central.

Palavras-Chaves: Suicídio, Tentativa de Suicídio, Colesterol, Triglicerídeos, Leptina, BDNF, PCR, S100B, IMC (índice de massa corporal), CC (circunferência da cintura).

ABSTRACT

Objective: Suicide is a public health problem of high complexity. Many peripheral markers have been searched for greater understanding of suicidal behavior. Cholesterol and its fractions were proposed as a biomarker for this condition. Herein, we analyzed the serum lipid profile, CRP (C-reactive protein), BDNF (Brain-derived neurotrophic factor), S100B and leptin in subjects with mood disorders (bipolar or major depression) diagnostic with a recent suicide attempt and in subjects with same diagnostic and no lifetime history of suicide attempt.

Methods: A total of 86 subjects with mood disorders were included in this study. Fifty subjects presented an episode of suicide attempt in the last 15 days, and thirty-six subjects had no history of suicide attempt. Serum lipid profile was evaluated by the content of total cholesterol, HDL, LDL and triglycerides.

Results: After adjusting for length of illness and of current episode, sex, use of anticonvulsants and SSRI (selective serotonin reuptake inhibitor), BMI (body mass index), and waist circumference, we found that triglycerides, BMI and waist circumference were decreased in subjects with suicide attempt when compared to subjects without suicide attempt. However, we found no differences between total cholesterol, LDL, HDL, leptin, BDNF, CRP and S100B between subjects with and without suicide attempt.

Conclusions: These data do not support the hypothesis that cholesterol and its fractions are associated with suicidal behavior in a sample of mood disorders patients. However, favor the idea that adiposity is differentiated in these patients with recent suicide attempt compared to patients without suicide attempt, suggesting an altered communication adipose tissue-central nervous system.

Keywords: Suicide, Attempted Suicide, Cholesterol, Triglycerides, Leptin, BDNF, CRP, S100B, BMI (body mass index), WC (waist circumference).

LISTA DE ABREVIATURAS E SIGLAS

5-HIAA	Ácido 5-Hidroxiindolacético
BDNF	Fator Neurotrófico Derivado do Encéfalo
CC	Circunferência da Cintura
CS	Comportamento Suicida
IL-1	Interleucina-1
IL-6	Interleucina- 6
IMC	Índice de Massa Corporal
LCR	Líquido Cefalorraquidiano
NGF	Fator de Crescimento Neural
NT-3	Neurotrofina-3
NT-4/5	Neurotrofina- 4/5
$p75^{NTR}$	Receptor Pan-Neurotrofina
PCR	Proteína C Reativa
SC	Suicídio Completo
TNF-α	Fator de Necrose Tumoral-α
Trk	Receptor de *Tropomiosina Cinase*
TrkA	Receptor Tirosina Cinase A
TrkB	Receptor Tirosina Cinase B
TrkC	Receptor Tirosina Cinase C
TS	Tentativa de Suicídio

1. INTRODUÇÃO

1.1. Conceitos básicos: suicídio, tentativa de suicídio e comportamento suicida.

Com o avanço nas pesquisas direcionadas para a compreensão do comportamento suicida e busca de mecanismos efetivos de prevenção, tornou-se evidente que um dos obstáculos a ser superado diz respeito justamente a definições e terminologia com uso diverso, muitas vezes dificultando a comunicação e interpretação de dados entre pesquisadores. Visando uma linguagem mais universal, discussões ganham espaço em debates e publicações em busca de um consenso quanto à padronização da nomenclatura (O'CARROLL et al., 1996; DEAR, 1997; MARUSIC, 2004; SILVERMAN et al., 2007; MATARAZZO et al., 2013). Para a proposta deste trabalho, as definições adotadas estão descritas a seguir.

O suicídio é um fenômeno complexo, resultado final de um *continuum* conhecido como comportamento suicida, onde estão incluídos o suicídio, tentativas de suicídio e pensamentos ou ideação suicida. O conceito de suicídio segundo a Organização Mundial de Saúde (<http://www.who.int/topics/suicide/en/>) é tecnicamente simples e direto: "*Suicide is the act of deliberately killing oneself.*". Enquanto tentativa de suicídio é conceituada como: "*a potentially self-injurious behavior with a nonfatal outcome, for which there is evidence (either explicit or implicit) that the person intended at some level to kill himself/herself; a suicide attempt may or may not result in injuries*" (O'CARROLL et al., 1996; NORDSTRÖM et al., 1995b). A ideação ou pensamentos suicidas se referem à vontade de morrer, incluindo o desejo de tirar a própria vida, aqui inserida como parte do comportamento suicida.

1.2. Epidemiologia Geral do Comportamento Suicida

“Gutta cavat lapidem non vi, sed saepe cadendo." Ovídio.

(“A gota escava a pedra, não pela violência, mas por cair freqüentemente”)

O suicídio tem sido foco de estudo e discussão ao longo do tempo em várias áreas do conhecimento, mas continua como importante causa de morte em todas as idades e responsável pela interrupção prematura de aproximadamente um milhão de vidas a cada ano (FURCZYK et al., 2013; KANG et al., 2013).

Apesar de todos os esforços seguimos buscando compreender o que leva uma pessoa a abdicar do seu direito a vida e nos deparamos com estatísticas que demonstram números crescentes de óbito tendo o suicídio como causa. Esta situação torna inegável a necessidade de encontrarmos métodos mais efetivos de reconhecimento e prevenção de novos casos.

Em 1999, a OMS expôs através de gráficos em seu *website* a evolução de óbitos por suicídio entre os anos de 1950 e 1995, mostrando aumento aproximado de 49% nas taxas de suicídio para homens e 33% nas taxas para mulheres, com o registro de 900.000 óbitos naquele último ano, com 10 a 20 vezes mais tentativas e uma estimativa global para 2020 de 1,53 milhões de vidas perdidas (BERTOLOTE e FLEISCHMANN, 2002). Sensíveis a estes dados, muitos órgãos tem lançado campanhas e cartilhas buscando a conscientização dos diversos segmentos da sociedade para a importância da detecção de risco e encaminhamento adequado e pertinente a cada situação (MINISTÉRIO DA SAÚDE, 2006; OMS, 2000a, 2000b, 2000c). A OMS alçou a prevenção ao suicídio como uma prioridade para a saúde pública. Entre outras medidas, em 1999 lançou o SUPRE (*Suicide Prevention Program*) (FLEISCHMANN et al., 2008; BERTOLOTE e DE LEO, 2012). Dados publicados no *site* da OMS, referentes ao ano de 2012, apontam o suicídio como responsável por 1,4% de todas as mortes no mundo, correspondendo a 15º posição dentro das principais causas de

morte, entretanto, a segunda principal causa de óbito entre as idades de 15 e 29 anos, sendo que 75% ocorreram em países de baixa e média (<http://www.who.int/topics/suicide/en/>). A taxa média de suicídio no mundo é de 11,6 por 100 mil habitantes, sendo que países asiáticos respondem por aproximadamente 60% destes (VARNIK, 2012; CHEN et al., 2012).

Apesar de grandes esforços e valiosas informações, a compreensão do(s) mecanismo(s) fisiopatológico(s) implicado(s) no surgimento do pensamento suicida e sua progressão até a morte auto infligida ainda não é suficiente para gerar condutas mais eficazes de prevenção e detecção precoce. A concepção da existência de uma base patológica para o comportamento suicida é justificada por estudos que tem demonstrado a presença de doença psiquiátrica em mais de 90% destes indivíduos na época do óbito (HENRIKSSON et al., 1993; CONWELL et al., 1996; FOSTER et al., 1997; HARRIS e BARRACLOUGH, 1997 ; CAVANAGH et al., 1999; VIJAYAKUMAR e RAJKUMAR, 1999; LECRUBIER, 2001; ZALSMAN et al., 2006; NOCK et al., 2009). O diagnóstico de desordens do humor está presente em aproximadamente 60% dos casos de suicídio associados a patologia psiquiátrica (PANDEY, 2013).

As taxas de suicídio variam ao redor do mundo, porém, os suicídios completos (SC), na população geral, apresentam características que se repetem com maior frequência na maioria dos países, sendo mais elevadas em homens, indivíduos idosos e caucasianos (POMPILI et al., 2013). Quanto ao comportamento suicida não-fatal (tentativa de suicídio, TS), não existem registros mundiais oficiais principalmente pelo fato de que somente cerca de 25% dos que tentam o suicídio precisam e/ou buscam atenção médica, a maioria das TSs, portanto, permanece não relatada e não registrada. A história pessoal de TS é reconhecida como um importante fator preditor para comportamento suicida futuro (BECK e STEER, 1989; CULLBERG et al., 1988; CHRISTIANSEN e JENSEN, 2015; FAWCETT et al.,

1990; NORDSTRÖM et al., 1995a; KESSLER et al., 1999; SUOKAS et al, 2001; OQUENDO et al., 2004; FLEISCHMANN et al., 2008; VIDAL, 2013).

O estudo sobre o comportamento suicida abre constantemente caminhos que levam a mais perguntas do que propriamente respostas, reforçando a ideia de múltiplos fatores confluindo para o surgimento de pensamentos suicidas e sua evolução para o planejamento, ou não, em situações que envolvem impulsividade, e consumação do ato.

O acesso mais recente a informações sobre países asiáticos tem mostrado algumas diferenças das tendências globais, como baixa prevalência de doença mental (DE LEO et al., 2009; CHEN et al., 2012) e baixa razão homem/mulher comparado a países ocidentais onde a taxa de suicídio é 3 a 4 vezes maior em homens do que mulheres (CHEN et al., 2012); particularmente na China, as taxas de suicídios em mulheres foi em média 25% maior que em homens, atribuída a alta frequência de suicídio em mulheres jovens residentes na zona rural (período de 1995 a 1999) (PHILLIPS, 2002); as taxas de suicídio na população idosa (≥ 65 anos) também são bastante elevadas na China continental, atingindo 44,3 a 200 por 100.000 (LI et al., 2009).

Entre pacientes psiquiátricos, aqueles com diagnóstico de transtorno de humor bipolar possuem alto índice de suicídio, cerca de 20 vezes mais que na população geral (TONDO et al., 2003). Estudos têm identificado que o comportamento suicida geralmente ocorre durante episódios depressivos ou mistos (ISOMETSÄ, 2014). É estimado que entre 25% e 50% dos pacientes com desordem bipolar tentarão suicídio no mínimo uma vez durante seu ciclo de vida, sendo que de 8% a 19% atingirão seu objetivo (MARANGELL et al. 2006).

1.3. **Epidemiologia do Comportamento Suicida no Brasil**

Há um consenso geral que o suicídio é um importante problema de saúde pública mundial, incluindo o Brasil. Comparando as taxas de suicídio de diferentes países, a taxa de mortalidade por suicídio no Brasil é uma das menores, mas em números absolutos está entre os dez países com o maior número de mortes por essa causa, correspondendo a 60.637 óbitos entre 2003 e 2009, equivalendo a 24 suicídios/dia (coeficiente médio: 4,5/100.000 habitantes) (VIDAL, 2013). Considerando o período de 1980 a 2012 foram registrados 216.211 casos (WAISELFISZ, 2014). Há uma estimativa de que para cada caso de suicídio existam pelo menos dez pessoas que tentaram suicídio e necessitaram atendimento médico, e que para cada tentativa existem quatro que não foram documentadas (VIDAL, 2013). Além disto, tem havido um aumento progressivo nas mortes por este meio nos últimos anos. Embora na década de 80 praticamente não tenha havido crescimento (2,7%), este foi de 18,8% na década de 90 e seguindo até 2012 o aumento foi de 33,3% (WAISELFISZ, 2014).

O Brasil é um país com dimensões continentais, representando 47% da América do Sul (PAIM et al., 2011). Dividido em cinco regiões, estas apresentam variações em suas taxas de suicídio - número de mortes por 100 mil habitantes no período de um ano, provavelmente resultante da influência de diferentes características históricas, socioculturais e econômicas, conferindo peculiaridades próprias a cada uma. Considerando o ano de 2012, o Rio Grande do Sul teve as maiores taxas de suicídio na população geral, após vem Santa Catarina, Mato Grosso do Sul e Roraima (10.9, 8.6, 8.4 e 8,1/100 mil habitantes, respectivamente; Brasil 5.3/100 mil habitantes), enquanto que Rio de Janeiro, Amapá e Pará apresentam as menores taxas (2.9, 3.0 e 3.1/100 mil habitantes); na população jovem (considerado de 15-29 anos), Roraima, Mato Grosso e Acre apresentam as maiores taxas de suicídio (12.9, 12.1 e 10.4/100 mil habitantes; Brasil 5.6/100 mil habitantes), enquanto que

Rio de janeiro, Bahia e Rio Grande do Norte as menores (2.5, 3.5 e 3.8/100 mil habitantes) (WAISELFISZ, 2014).

1.4. Biomarcadores

“The art of simplicity is a puzzle of complexity.”

Doug Horton (1891-1968)

Como definido por *Biomarkers Definitions Working Group* (2001): “Biomarcadores são indicadores de processos biológicos normais, processos patogênicos ou respostas farmacológicas para uma intervenção terapêutica, que podem ser medidos e avaliados objetivamente”. Com a perspectiva de contribuir para uma melhor compreensão dos mecanismos subjacentes a instalação da ideação suicida até a progressão para a letalidade, foram propostos prováveis Biomarcadores para o comportamento suicida, considerando o conjunto de informações já disponíveis e as possíveis relações entre eles.

A neurobiologia do comportamento suicida permanece em grande parte por ser elucidada, sua complexidade refletindo sua natureza multifatorial. Nestas condições, a possibilidade de pesquisar e correlacionar dados biológicos em materiais como líquor, plasma, soro, urina e outros, poderá contribuir para o desenvolvimento de abordagens terapêuticas mais efetivas e com maior eficácia em prevenção, considerando que a avaliação de fatores de risco clínicos não demonstra um valor preditivo seguro o que reforça a importância das pesquisas direcionadas a marcadores (COSTANZA et al., 2014).

Assim, serão abordados: colesterol total e frações, triglicerídeos, PCR (proteína C reativa), BDNF (fator neurotrófico derivado do encéfalo), S100B e leptina.

1.4.1. Colesterol Total e Frações

Desde a descoberta do colesterol, em 1815, pelo químico francês Michel Eugène Chevreul (GOEDEKE e FERNÁNDEZ-HERNANDO, 2012), muitas informações surgiram e muitos questionamentos persistem. As pesquisas tem gerado conhecimento crescente sobre esta molécula, como os mecanismos de aquisição celular e regulação de seu metabolismo até constatações mais recentes como sua interação com membros da família das anexinas (DOMON et al., 2012). O encéfalo é o local com maior quantidade de colesterol em nosso organismo, contendo aproximadamente 10 vezes mais que qualquer outro órgão, uma média de 70% está presente na mielina, 20% nas células gliais e 10% em neurônios (BJÖRKHEM et al., 2010). Também é o principal constituinte das membranas fosfolipídicas de nossas células, modulando fluidez e permeabilidade (PFRIEGER, 2003; WATERHAM, 2006; VYROUBAL, 2008; AQUL, 2011; DOMON et al., 2012), e precursor de componentes vitais como hormônios esteroides, ácidos biliares e vitamina D_3 (7-dehidrocolesterol/colecalciferol) (GLOSSMANN, 2010; TIEU et al., 2012). Estudos têm investigado a participação do colesterol em processos celulares como sinalização, transporte vesicular, interação com patógenos, entre outros (PFRIEGER, 2003; VYROUBAL et al., 2008; DOMON et al., 2012).

Referências históricas sobre o papel do colesterol no campo da saúde mental podem ser encontradas em publicações tão antigas como a de Paul G. Weston (1915) e de Cruickshank e Tisdall (1916). Completando 100 anos, o trabalho de Paul G. Weston descreveu diferenças encontradas na quantidade média do colesterol no líquor de pacientes com diferentes diagnósticos, por exemplo, pacientes com "demência precoce" (correspondendo à esquizofrenia) apresentaram valores superiores aos pacientes com psicose maníaco-depressiva (corespondendo ao transtorno de humor bipolar) (WESTON, 1915). Em artigo intitulado "The Cholesterol Content of the Serum in Mental Diseases",

Cruickshank e Tisdall (1916) descreveram os valores de colesterol encontrados no soro de 40 pacientes com transtorno mental, o planejamento inicial da pesquisa incluía a dosagem também em suprarrenal e bile, mas foi impedido pela destruição dos materiais em decorrência da Primeira Guerra Mundial e partida do Dr. Tisdall para o serviço militar. Em 1933, A. Glen Duncan reuniu várias pesquisas realizadas no antigo *Severalls Mental Hospital*, localizado na cidade britânica de Colchester, também direcionadas à busca de uma relação entre colesterol e transtornos mentais; ao final, sua conclusão: "Conclui-se que o colesterol é um dos fatores de controle do metabolismo celular e que os neurônios são suscetíveis a alterações quantitativas desta substância no seu ambiente" (DUNCAN, 1933). Em estudo publicado em 1969, foram medidos os níveis séricos de colesterol total em 03 pacientes com "catatonia periódica" e os resultados foram assim descritos: "O colesterol total diminuiu durante a fase psicótica e aumentou durante a fase de intervalo. Atingiu o valor máximo no final da fase de intervalo ou no início da fase psicótica" (MAEDA et al., 1969). A primeira referência a um possível elo entre níveis de colesterol sérico baixo e morte violenta, isto é, não resultante de uma patologia ou morte como término natural do ciclo da vida, surgiu em 1969, na publicação dos resultados de um estudo clínico controlado destinado a avaliar a influência da dieta no risco de doença cardiovascular (DAYTON et al., 1969). Em sequência, óbitos por injúria também ocorreram durante estudo com pacientes recebendo colestiramina (MANFREDINI et al., 2000), medicação utilizada na terapia de redução do colesterol (GUPTA et al., 2010). Muitos estudos têm associado colesterol sérico baixo e sintomas psiquiátricos, especialmente suicídio (TROISI, 2009). Entre os poucos estudos que diferenciam as frações do colesterol, o comportamento suicida e impulsividade foram associados a baixos níveis de LDL-C (l*ow-density lipoprotein cholesterol*) (LEE e KIM, 2003; AGARGUN et al., 2004; GARLAND et al., 2007; MARCINKO et al., 2008) enquanto baixos níveis de HDL-C (*high-density*

lipoprotein cholesterol) foram fortemente associados com sintomas depressivos (TROISI, 2009).

1.4.2. Proteína C Reativa (PCR)

Na história da medicina ocidental encontramos Aulus Cornelius Celsus (25 aC – 50 dC), enciclopedista contemporâneo de Jesus Cristo, com vasto conhecimento de medicina e cirurgia, quem primeiramente descreveu os quatro sinais cardinais da inflamação: "*Notae vera inflammationis sunt quattuor; rubor et tumor cum calore et dolore*" ("Os sinais de inflamação grave são quatro: vermelhidão e inchaço com calor e dor") (FORREST, 1982). Muitos pesquisadores têm buscado e demonstrado uma associação entre patologias psiquiátricas e inflamação. Mas quais seriam então os sinais clínicos que poderiam estar expressando esta inflamação do encéfalo ou de segmentos dele? Ouvimos falar em "dor da alma", mas não dor no encéfalo. Seriam a tristeza, a ansiedade, o medo e tantas outras emoções expressões da dor de um órgão que não pode ser comumente visto e examinado como uma úlcera ou ferida aberta? Poderiam então os sintomas psiquiátricos corresponderem aos sinais cardinais de Celsus? Ou, mais especificamente, corresponderem a dor como sintoma decorrente do surgimento e evolução de uma doença inflamatória? Considerando como um fato a presença de um processo inflamatório no Sistema Nervoso Central (SNC) ainda assim teremos que responder se este é o fator inicial ou uma reação secundária a outro evento agressor, também por ser identificado.

Dentro deste contexto, a proteína-C reativa (PCR) surge como um possível biomarcador para o comportamento suicida. A PCR foi a primeira proteína de fase aguda a ser descrita, assim denominada por sua capacidade de reagir e precipitar o polissacarídeo C extraído da parede celular e da cápsula da bactéria *Streptococcus pneumoniae* (Pneumococo) (TILLETT e FRANCIS, 1930). Apesar de ser reconhecida como resposta de

fase aguda, as mudanças sistêmicas ocorrem tanto em distúrbios inflamatórios agudos quanto crônicos (GABAY e KUSHNER, 1999).

A síntese da PCR ocorre no fígado por estímulo direto de interleucina 1 (IL-1), interleucina 6 (IL-6) e fator de necrose tumoral-α (TNF-α) (BERK et al., 1997; MORTENSEN, 2001; AL-KARKHI et al., 2013). Já considerada um marcador-chave para inflamação por sua significativa sensibilidade (PEPYS e BALTZ, 1983; WEUVE et al., 2006), sua dosagem pode ser facilmente aplicada na prática médica diária por ser de custo financeiro acessível permitindo maior abrangência populacional. Níveis elevados de PCR têm sido descritos tanto na presença de estresse crônico (MILLER et al., 2009) quanto em vários transtornos mentais como em esquizofrenia (GARCIA-RIZO et al., 2012; WIUM-ANDERSEN et al., 2014; MILLER et al., 2014), incluindo intensidade dos sintomas (FAN et al., 2007); em quadros depressivos (MAES et al., 1997; BERK et al., 1997; FORD e ERLINGER, 2004; PASCO et al., 2010; AZAR e MERCER, 2013); em pacientes com elevada ideação suicida (O'DONOVAN et al., 2013). Por outro lado, alguns achados sugerem que a utilização de medicações psicotrópicas possa atuar normalizando a resposta imune sistêmica (HORNIG et al., 1998).

1.4.3. Fator Neurotrófico Derivado do Encéfalo (BDNF)

O fator neurotrófico derivado do encéfalo (BDNF- *brain derived neurotrophic factor*) é parte integrante da família de neurotrofinas, a qual pertence outras importantes proteínas como fator de crescimento neural (NGF- *nerve growth factor*), a neurotrofina-3 (NT-3) e neurotrofina- 4/5 (NT-4/5) (ICHIM et al., 2012; NUMAKAWA et al., 2014). As neurotrofinas são proteínas secretadas cuja atividade biológica ocorre através de ligação a duas classes diferentes de receptores, uma de alta afinidade, que são os receptores de tropomiosina cinase (Trk), da família tirosina cinase, composta por TrkA (para NGF), TrkB (para BDNF e NT-4/5) e TrkC (para NT-3), e do receptor $p75^{NTR}$ (DWIVEDI, 2010;

ICHIM et al., 2012; PASKA et al., 2013), parte da superfamília de receptores do fator de necrose tumoral (TNF- *tumor necrosis factor*) e não seletivo, permitindo a ligação de todas as neurotrofinas (ICHIM et al., 2012).

O BDNF possui elevado nível de expressão no encéfalo, mas também perifericamente (LEE et al., 2007), possuindo papel fundamental para a sobrevivência e plasticidade neuronal, sendo que pesquisadores tem sugerido alteração da plasticidade de circuitos neuronais como um fator crucial na fisiopatologia do suicídio, respaldados por pesquisas cujos resultados tem relacionado esta neurotrofina, direta ou indiretamente, ao comportamento suicida (PREGELJ et al., 2011; ZAI et al., 2012; KANG et al., 2013; PASKA et al., 2013).

Estudos *post-mortem* têm contribuído para a expansão do conhecimento dos mecanismos subjacentes envolvidos no comportamento suicida, como achados de expressão reduzida de BDNF, níveis de proteínas e de RNAm, e do TrkB em hipocampo e córtex pré-frontal de vítimas de suicidio (DWIVEDI et al., 2003); expressão proteica diminuída de BDNF e do receptor TrkB isoforma completa em córtex pré-frontal, assim como de TrkB em hipocampo, de vítimas adolescentes (PANDEY et al., 2008); níveis reduzidos de BDNF em córtex pré-frontal e em hipocampo também de suicidas (KAREGE et al., 2005).

1.4.4. Leptina

A leptina é uma proteína sintetizada pelo adipócito, célula armazenadora de gordura, e codificada pelo gene *ob*. Graças a sua descoberta, o tecido adiposo tem sido reconhecido como um órgão endócrino, produtor de peptídeos ativos biologicamente conhecidos por adipocinas (WĘDRYCHOWICZ et al., 2014). Resumidamente, através de sua interação com hipotálamo, mais especificamente com receptores localizados em neurônios do núcleo arqueado, o aumento da concentração da leptina desencadeia a ativação de neurônios do núcleo paraventricular com subsequente resposta humoral representada pela

secreção de TSH (Hormônio Estimulador da Tireóide) e de ACTH (Hormônio Adrenocorticotrófico). Numa cascata de eventos, ocorre o aumento da taxa metabólica e regulação da ingestão alimentar culminando com a homeostase da gordura e da massa corporal (ROBERTSON et al., 2008). Em outras palavras, a leptina atua como um sinal aferente modulando a ingestão de alimentos e equilibrando o peso corporal. Outra possível ação parece ser a modificação da concentração lipídica intracelular por redução da síntese de ácidos graxos (ATMACA et al., 2003). Esta proteína vem despertando interesse em relação a sua possível participação na fisiopatologia das desordens psiquiátricas, como em comportamento suicida (ATMACA et al., 2002, 2003, 2008).

1.4.6. S100B

Tradicionalmente, as células gliais são reconhecidas como elementos fundamentais da estrutura e de homeostase iônica. Há alguns anos, vem sendo pesquisado seu envolvimento ativo na transmissão sináptica e plasticidade neuronal, mais especificamente através da atividade de uma proteína ligante de cálcio chamada S100B, produzida e secretada pelos astrócitos, o maior subtipo de célula glial, e por alguns grupamentos neuronais (NISHIYAMA et al., 2002; SCACCIANOCE et al., 2004). A proteína S100B está presente tanto em tecido cerebral, em maior proporção, quanto extracerebral. Executa tanto funções regulatórias intracelulares, como a fosforilação de proteínas, quanto extracelulares, ainda não totalmente esclarecidas (DONATO, 2001). No encéfalo adulto, tem ação sobre a plasticidade neuronal e no potencial de longa duração, atuando sobre a extensão dos neuritos, estabilizando microtúbulos através da inibição da fosforilação de proteínas do citoesqueleto cerebral como MAP2, Tau e GAP-43 (ROTHERMUNDT et al., 2004; NISH et al., 2000). S100B extracelular em baixas concentrações atua sobre a glia e células neuronais como um fator de crescimento e diferenciação, porém, em concentrações elevadas mostrou desencadear apoptose celular (FANO et al., 1995). Entre as ações desta proteína

parece estar a estimulação de resposta inflamatória vascular através da interação com receptores RAGE (*advanced glycation end products*) (OHTAKI et al., 2007).

A S100B tem sido incluída na busca de possíveis marcadores para uma série de patologias, das neoplasias, como o melanoma (LIN et al., 2004), como indicador de risco para transformação hemorrágica após terapia trombolítica em pacientes que sofreram isquemia cerebral (FOERCH et al., 2007), chegando às doenças mentais. Autores que focam as fontes extracerebrais da proteína S100B entendem que possivelmente não se trata de um marcador específico do SNC. Nosso grupo, na Universidade Federal do Rio Grande do Sul, demonstrou ser o tecido adiposo, mais especificamente o adipócito, a segunda maior fonte provável desta proteína (NETTO et al., 2006; GONÇALVES et al, 2008). Atualmente, além das pesquisas focadas no sistema neuronal como centro dos transtornos mentais, outros locais relacionados têm estimulado estudos envolvendo a atividade glial e, mais recentemente, o papel do tecido adiposo como um órgão endócrino, ativo e em sintonia com o SNC. Com relação à S100B, sabe-se que tem sua liberação regulada pela serotonina através do receptor serotoninérgico $5HT_{1A}$ e elevações de seus níveis foram detectadas em modelos animais de estresse e em seres humanos com esquizofrenia e doença bipolar (ROTHERMUNDT et al., 2004; SCACCIANOCE et al., 2004). Estudos em ratos submetidos a estresse encontraram mudanças nos níveis desta proteína tanto em líquor (MARGIS et al., 2004) quanto em soro (SCACCIANOCE et al., 2004). Níveis séricos elevados de S100B foram encontrados em pacientes com desordem bipolar fora do período eutímico (ANDREAZZA et al., 2007). Em 2006, foi publicado um estudo de S100B em SNC de pessoas com diagnóstico de esquizofrenia e doença bipolar tipo 1 quando foi evidenciada uma elevação dos níveis de S100B em área cortical 40 de tecido proveniente de indivíduos bipolares (DEAN et al., 2006). Como referido anteriormente, a liberação de S100B é dependente da ação agonista nos receptores $5HT_{1A}$ (WHITAKER-AZMITIA et al,

1990). Em outra pesquisa, o [^{3}H]8- hidroxy-2-(di-n-propyl) aminotetralin (8-OH-DPAT), um agonista do autoreceptor $5HT_{1A}$, mostrou um aumento significativo de ligação a estes receptores nos núcleos da rafe do mesencéfalo, mais especificamente subnúcleos dorsal e ventrolateral, de vítimas de suicídio com depressão maior quando comparados a controles normais (STOCKMEIER et al., 1998). Este achado reforça a hipótese de diminuição de atividade em neurônios serotoninérgicos em depressão e suicídio. Além disso, cultura de astrócitos e fatias hipocampais responderam a fluoxetina aumentando a secreção de S100B, aparentemente independentemente da serotonina e receptores serotoninérgicos (TRAMONTINA et al, 2008).

Pelo fato da proteína S100B estar alterada em uma diversidade de doenças neuropsiquiátricas e ter uma atividade *in vitro* que se assemelha a uma citocina, a S100B é comparável a proteína C reativa do sistema imunológico (SEN e BELLI, 2007). De fato, ambas estão alteradas no transtorno bipolar (CUNHA et al, 2008), doença psiquiátrica frequentemente relacionada a comportamento suicida.

2. OBJETIVOS

Com base na literatura existente percebe-se que a população com transtornos de humor tem um maior risco de suicídio e há uma hipótese corrente de que colesterol sérico baixo é um biomarcador de risco para suicídio. Com base nisso estabelecemos dois objetivos:

1. Revisar na literatura informações que pudessem conectar as alterações de colesterol observadas no soro com as alterações neuroquímicas observadas em pacientes suicidas ou com história de tentativa(s) de suicídio;
2. Avaliar em pacientes com transtorno de humor se é possível diferenciar o comportamento suicida com os níveis séricos de colesterol e frações, bem como outros supostos marcadores de risco para suicídio, como triglicerídeos, leptina, S100B, BDNF, PCR, IMC e CC.

3. MATERIAL E MÉTODOS

Uma descrição detalhada deste item encontra-se no artigo do Capítulo 02.

3.1. Amostra

A amostra foi colhida de forma consecutiva entre os pacientes internados na Clínica São José, instituição privada para atendimento de pacientes psiquiátricos na cidade de Porto Alegre (RS), no período entre abril de 2010 e dezembro de 2012. Aceitaram participar do estudo e assinaram o Termo de Consentimento Livre e Esclarecido um total de 86 pacientes com Transtorno de Humor, bipolares e unipolares. Destes, 50 haviam tentado suicídio até 15 dias antes das entrevistas e coletas. Outros 36 não possuíam história na vida de tentativa de suicídio.

3.2. Delineamento do Estudo

Após a assinatura do Termo de Consentimento, os pacientes participavam de uma entrevista com o examinador. Em um segundo momento, ocorria a coleta de sangue para análise.

3.3. Instrumentos

3.3.1. Entrevista Biopsicossocial: especialmente construída para a pesquisa, incluindo aspectos demográficos e história médica e ocupacional;

3.3.2. Mini-Exame do Estado Mental de Folstein: utilizando a versão de Brucki (2003);

3.3.3. *Mini International Neuropsychiatric Interview Plus* (MINI-PLUS);

3.3.4. Aferição de Peso, Altura, CC;

3.3.5. Coleta de 5 ml de sangue venoso, centrifugado (3000 rpm/5 min) e soro armazenado a -70º C.

4. RESULTADOS

Os resultados serão apresentados na forma de dois artigos, gerados por este estudo, cujas referências encontram-se abaixo:

CANTARELLI, M.G., TRAMONTINA, A.C., LEITE, M.C., GONÇALVES, C.A. Potential neurochemical links between cholesterol and suicidal behavior. Psychiatry Research. 2014; 220: 745-751.

CANTARELLI, M.G., NARDIM, P., BUFFON, A., EIDT, M.C., GODOY, L.A., FERNANDES, B.S., GONÇALVES, C.A. Serum triglycerides, but not cholesterol or leptin, are decreased in suicide attempters with mood disorders. Journal of Affective Disorders. 2015; 172: 403-409.

Capítulo 01

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Review article

Potential neurochemical links between cholesterol and suicidal behavior

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ABSTRACT

The role of cholesterol in psychiatric diseases has aroused the interest of the medical community, particularly in association with violent and suicidal behavior. Herein, we discuss some aspects of brain cholesterol metabolism, exploring possible mechanisms underlying the findings and reviewing the available literature on the possible neurochemical link between suicide and low or reduced levels of serum cholesterol. Most of the current hypotheses suggest a decreased serotonergic activity due to a decrease in cholesterol in the lipid rafts of synaptic membranes. Some aspects and limitations of this assumption are emphasized. In addition to serotonin hypofunction, other mechanisms have been proposed to explain increased impulsivity in suicidal individuals, including steroid modulation and brain-derived neurotrophic factor decrease, which could also be related to changes in lipid rafts. Other putative markers of suicidal behavior (e.g. protein S100B) are discussed in connection with cholesterol metabolism in the brain tissue.

Contents

1. Introduction

Suicidal behavior remains a major challenge for psychiatrists and other health care professionals. The suicide rate for the world as a whole is estimated at 11.6 per 100,000 inhabitants (Värnik, 2012). The WHO estimated that approximately 900,000 people die each year by suicide worldwide, mostly in countries of low and middle income (Patel et al., 2012) and predominantly in young (Hawton et al., 2012) and male individuals (Phillips and Cheng, 2012).

Suicide rates have increased in the young population, changing the risk profile, which is traditionally known as being directly proportional to the increase in age (Pitman et al., 2012). In fact, suicide is among the three most frequent causes of death in young people aged 10–24 or 15–44 years (Hawton et al., 2012; Yip et al., 2012). In Brazil, an epidemiological analysis of suicide rates performed by Lovisi and

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collaborators, from 1980 to 2006, showed a 30% increase in suicide rate during these 26 years, with higher average rates in the south and central-West regions. Teenagers and young adults of the Guarani-Kaiowá indigenous community represented a significant proportion of these deaths (Lovisi et al., 2009).

Suicidal behavior is a condition of high complexity, with different etiological factors and is still poorly understood. New approaches are needed to complement the fundamental vision of social influences, cultural and individual propensity to suicide. In particular, improved prevention strategies are required in addition to extensive scientific studies. Many researchers have focused on the search for biological markers that may be linked to suicidal behavior and can be used as an additional instrument for prevention and therapeutic actions.

The role of cholesterol in mental health has aroused the interest of the scientific community, due to its association with violent and suicidal behavior, as identified by a number of studies. As such, we discuss some aspects of brain cholesterol metabolism, exploring possible mechanisms underlying the findings and reviewing the available literature on the possible link between suicide and low or reduced levels of cholesterol.

2. Low serum cholesterol and suicidal behavior

A number of studies have investigated a possible link between low serum cholesterol and psychiatric symptoms, especially suicidal behavior (Troisi, 2009). These studies include cholesterol-lowering trials (e.g Nakamura et al., 2006), as well as cross-sectional (e.g. Zhang et al., 2005), case-control (e.g. Vuksan-Cusa et al., 2009) and cohort studies (e.g Boscarino et al., 2009). Among the few studies that differentiate the fractions of cholesterol, suicidal behavior and impulsivity have been associated with lower levels of low-density lipoprotein/cholesterol (Lee and Kim, 2003; Agargun et al., 2004; Garland et al., 2007; Marcinko et al., 2008), while low levels of high-density lipoprotein/cholesterol have been more strongly associated with depressive symptomatology (Troisi, 2009). The earliest mention of suicide in a clinical study designed to assess the influence of diet on cardiovascular disease risk probably occurred in the 1960s (Dayton and Pearce, 1969). Subsequently, deaths from injury were also recorded during a study with patients receiving cholestyramine (Manfredini et al., 2000), a cholesterol-lowering drug (Gupta et al., 2010), which may also decrease the concentration of essential polyunsaturated fatty acids (PUFA) (Hibbeln and Salem, 1996). It is important to mention that some authors claim that cholesterol is only a bystander for PUFA, which have been associated with depressive behavior (Liperoti et al., 2009). However, the association of brain PUFA levels in suicide cases is also not consistent (Lalovic et al., 2007).

A meta-analysis reported by Muldoon and collaborators in 1990 is often cited as a reference of critical importance with regard to demonstrating the association between low serum cholesterol, suicide and violent death. This study demonstrated a significant association between reductions in cholesterol and increases in death by suicide or accidental or violent death, regardless of how cholesterol levels were reduced (dietary or pharmacological use); although mortality from coronary heart disease has been reduced in the treated group, specifically those under pharmacologic action, total mortality was unchanged (Muldoon et al., 1990). It is important to point out that impulsive and aggressive behavior is a predisposing factor to accidents, trauma and suicidal behavior (Virkkunen et al., 1989; Muldoon et al., 1990; Romanov et al., 1994).

A prospective observational study in Chinese individuals with naturally low serum cholesterol levels found an inverse association between deaths not related to illness, including suicide, and serum cholesterol, although this was considered by the authors as "marginally significant" (Chen et al., 1991). Since then, a succession of studies have sought to determine whether low serum levels of cholesterol are a risk factor for suicidal behavior. Epidemiological, clinical and biochemical data have provided important information on this theme, although not conclusive, but these data may be important for understanding the mechanism at play. Many studies provide data to support the existence of this association (Lindberg et al., 1992; Neaton and Wentworth, 1992; Kunugi et al., 1997; Partonen et al., 1999; Almeida-Montes et al., 2000; Ellison and Morrison, 2001; Tamosiunas et al., 2005; Garland et al., 2007; Boscarino et al., 2009); however, other studies have found no relationship (Smith et al., 1992; Seneviratne et al., 1999; Steinert et al., 1999) and others have identified an increased risk of violent death by suicide in the presence of elevated serum cholesterol (Tanskanen et al., 2000).

Case-control studies developed in clinical populations have often shown that individuals with past suicide attempts had lower levels of serum cholesterol, compared to patients without the same history (Guillem et al., 2002; Kim et al., 2002; Atmaca et al., 2003; Lee and Kim, 2003; Favaro et al., 2004; Kim and Myint, 2004; Fiedorowicz and Coryell, 2007; Marcinko et al., 2008); again the findings are not unanimous, with negative results regarding this association reported (Apter et al., 1999; Almeida-Montes et al., 2000; Huang and Wu, 2000; Roy et al., 2001; Deisenhammer et al., 2004; Huang, 2005; De Leon et al., 2011. It is important to mention, at this time, that the low cholesterol referred to throughout this text does not necessarily constitute hypocholesterolemia, which is defined as total cholesterol and low density protein/cholesterol levels of below the 5th percentile of the general population, when adjusted for age, gender and race (Moutzouri et al., 2011). The 5th percentile of total cholesterol for adult men in USA ranges from 3.39 to 3.98 mmol/L and the 5th percentile of cholesterol in low density protein is approximately 2.33 nmol/L.

With regard to the genetic aspects of cholesterol homeostasis, some genes may be considered as candidates for the investigation of suicidal behavior (Gietl et al., 2007). Among the causes of hypocholesterolemia is the syndrome of Smith–Lemli–Opitz, an autossomal recessive disorder, where cholesterol synthesis is impaired due to 7-dehydrocholesterol reductase deficiency (DeBarber et al., 2011; Hayashi, 2011; Pfrieger and Ungerer, 2011). A family history of suicidal behavior is frequent among carriers of Smith–Lemli–Opitz syndrome (Lalovic et al., 2004), reinforcing the link between low cholesterol and suicidal behavior. Another candidate is ABCG1, a transporter of sterols across cell membranes (Schmitz et al., 2001). Five variants of ABCG1 gene were investigated in suicide attempters and completers, suggesting a connection of this gene with the aggression-related trait of these individuals (Gietl et al., 2007).

Two meta-analyses summarize our current knowledge about cholesterol and suicidal behavior; follow-up studies found that those individuals with lower cholesterol levels do have a slightly, but statistically significant, increased risk of completing suicide (Lester, 2002); however, there is no evidence indicating that non-illness mortality (including accidents, trauma and suicide) is increased significantly by cholesterol-lowering treatments (Muldoon et al., 2001).

Moreover, more recently other serum lipid changes beyond cholesterol have been associated with violent and non-violent suicide attempt suggesting the necessity of observing signals of altered adiposity in these individuals (Baek et al., 2014; Park et al., 2014). It is also noteworthy that serum cholesterol is affected by age, gender, nutritional status, and in the case of psychiatric patients (frequently linked with suicide risk), cholesterol levels are also affected by medication and lifestyle (e.g. smoking, alcohol use and sedentary). All these elements are confounder factors and demand a careful adjustment in statistical analyses. For example, a

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number of cross-sectional studies that found a negative correlation between serum cholesterol and suicidality were not adjusted for body weight or body mass index (Zhang and Li, 2011).

3. Brain cholesterol contributes to neurosteroid synthesis and lipid raft formation.

Brain cholesterol represents 25% of the body cholesterol and it is, apparently, synthetized independently from the extra-brain sources (Dietschy, 2009). More than 70% of the cholesterol found in myelin is formed by the oligodendrocytes. Astrocytes and microglia contain 20% and neurons 10% of brain cholesterol. During embryonic development, newborn neurons produce their own cholesterol, but mature neurons depend on astrocytic sources (Pfrieger and Ungerer, 2011). Extra-brain cholesterol does not cross the blood–brain barrier and, therefore, the absence of a direct biochemical relationship between peripheral and brain cholesterol makes it difficult to interpret changes in behavior from changes in peripheral cholesterol. However, there is some experimental evidence to suggest that extra-brain cholesterol influences brain activity (Schreurs, 2010). For example, elevated blood cholesterol has many peripheral consequences, which could signal to the brain via metabolites of cholesterol (e.g. 27-hydroxycholesterol). As such, this issue is very complex and the literature presents conflicting results regarding this issue (Zhang and Li, 2011).

Astrocytes produce enzymes for cholesterol synthesis and also express the apolipoproteins necessary to export cholesterol to the neurons, ApoE, ApoD and ApoJ (also called clusterin), but they do not express apolipoprotein B. These astrocyte proteins are upregulated during brain injury (Terrisse et al., 1999; Iwata et al., 2005). In addition, in astrocyte cultures, various neurotransmitters (e.g. serotonin) (Cedazo-Mínguez et al., 2001) and neuromodulators (e.g. guanosine) (Ballerini et al., 2006) seem to be involved in cholesterol and ApoE secretion (see Fig. 1A).

The astrocyte-derived lipoproteins have densities that are similar to those of peripheral HDL and contain cholesterol (mainly non-esterified) and some precursors (e.g. desmosterol), suggesting that neurons could convert these to cholesterol (Wang et al., 2008). The neuron uptake of these lipoproteins depends on the prototypic low-density lipoprotein receptor (LDLR) and LDL-related protein 1(LRP1), which bind ApoE. LRP1 is predominantly expressed by neurons, while LDLR is also expressed by glial cells.

Together with sphingolipids and gangliosides, cholesterol is concentrated in detergent-resistant microdomains (less than 0.1 μm) of the membrane called lipid rafts (Simons and Toomre, 2000). Lipid rafts have been implicated in several processes, such as the coordination of signal transduction, since they can promote interactions between signaling molecules (Pike, 2003). Lipid rafts are also involved in intracellular trafficking, where they have an important role in non-classic forms of endocytosis (Lajoie and Nabi, 2007); this process appears to be very sensitive to cholesterol levels reduction (Parton and Richards, 2003). Another function of lipid rafts is to provide communication with the cytoskeleton, as indicated by the fact that several cytoskeleton proteins have been isolated from rafts (Pike, 2009). As such, since cholesterol is an essential compound of lipid rafts, and any alteration in its content can modify the actions cited above.

A schematic lipid raft containing serotonin receptors is shown in Fig. 1B. The saturated acyl groups allow cholesterol to be packed in these domains that concentrate receptors, kinases, phosphatases and G proteins, involved in signal transduction. Until now, no specific protein sequences have been identified to explain their localization in such domains, but some of them bind to cholesterol through a cholesterol recognition amino acid consensus (CRAC) motif (e.g. $5HT_{1A}$ receptor) (Jafurulla et al., 2011). Caveolin is a CRAC-containing protein, found in a subset of lipid rafts and responsible for the formation of invaginated structures called caveolae (Epand et al., 2005). Caveolin interacts and works a scaffold for other proteins such as dopamine receptor 1 (Kong et al., 2007). It has been reported that glutamatergic, gabaergic, dopaminergic, serotoninergic, cholinergic and purinergic neurotransmissions are affected by cholesterol depletion in lipids rafts (see Sebastião et al. (2013) for a review). Therefore, again, alterations in cholesterol levels could affect lipid raft activity and thus changing synaptic transmission and neural plasticity, in turn, leading to brain disorders.

Besides its function in membranes, brain cholesterol is a precursor for the synthesis of a number of important molecules, including neurosteroids and the oxysterol, 24S-hydroxycholesterol. This oxysterol is produced by the enzyme cholesterol 24-hydroxylase, which is only expressed in neurons. This compound is released by neurons

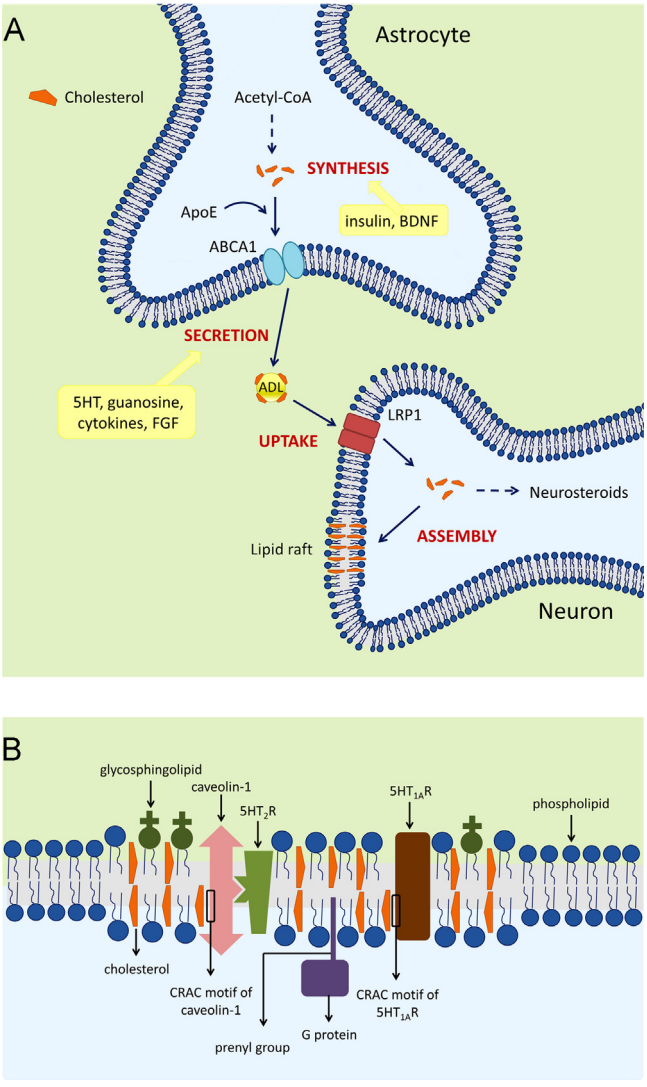

Fig. 1. In A, Schematic representation of cholesterol flux between astrocyte and neurons. Cholesterol is synthetized from acetyl-CoA in astrocytes (under the control of HMG-CoA reductase). Notice that, in the brain, insulin and BDNF modulate cholesterol synthesis. ATP-binding cassette A1 transporter (ABCA1) is indicated in the lipid assembly for ADL (astrocyte-derived lipoprotein). ApoE is the main apolipoprotein for ADL and its secretion is stimulated by several local indicated mediators (5HT, guanosine, FGF and cytokines). ADL is uptaken by neurons through LPR1 and released cholesterol is used for neurosteroid synthesis and lipid raft assembly. In B, Schematic representation of the lipid raft containing serotonin receptors. Cholesterol is packed between the saturated chains of glycerophospholipids and glycosphingolipids. Caveolin-1 interacts directly with cholesterol thorough the CRAC (cholesterol recognition amino acid consensus) motif. Serotonin receptor 1A binds to cholesterol also through a CRAC motif, while serotonin receptor 2A binds to Caveolin-1. G proteins are attached to the membrane by a prenyl group (an intermediate of cholesterol synthesis).

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and regulates the synthesis of ApoE in astrocytes (see Leoni and Caccia (2011), for a review) and, interestingly, an increment of 24S-hydroxycholesterol was reported in prefrontal cortex of suicide cases (Freemantle et al., 2013). Neurosteroids are able to modulate neuronal excitability through NMDA and GABA receptors (see Korinek et al. (2011) for a review). Under physiological conditions, neurons are the major sources of neurosteroids, initially converting cholesterol to pregnenolone, a step catalyzed by the cytochrome P450 cholesterol-side chain cleavage enzyme (P450scc). However, reactive astrocytes formed in response to brain injury could express high levels of P450scc (Biagini et al., 2009), assuming an important role in neurosteroid synthesis. These cholesterol-derived compounds have been proven to have a significant modulatory effect on ionic receptors; both at the cellular and behavioral level, and alterations in brain cholesterol metabolism could underlie a number of brain disorders.

4. Cholesterol and suicidal behavior: neurochemical connections

Although a correlation between low serum cholesterol and suicidal behavior has been observed in some clinical studies and a biochemical link between brain cholesterol and brain activity is proposed, it remains to be identified whether and how peripheral cholesterol affects brain cholesterol. Moreover, this association has been found to be even greater in individuals who had attempted suicide using violent methods. Low 5HT is central to the biology of violence (Vevera et al., 2003). In fact, in vivo and *postmortem* studies indicate serotonergic hypofunction in suicide and serious suicide attempts. This reduced activity leads to a predisposition to impulsive and aggressive behavior, probably due to a breakdown in the inhibitory function of the ventral prefrontal cortex as a result of lower serotonin input (Kamali et al., 2001).

Most of the current hypotheses suggest a decreased serotonergic activity due to a decrease of cholesterol in lipid rafts. In fact, experimental depletion of cholesterol leads to a decrease in $5HT_{1A}$ binding, G protein coupling (Pucadyil and Chattopadhyay, 2004) and downstream signaling (Sjögren et al., 2008). Other serotonin receptors are localized in lipid rafts binding to caveolin-1 (e.g. $5HT_{2A}$) or not (e.g. $5HT_{7A}$), as well as serotonin transporters (Magnani et al., 2004). In support of these findings, lower grey-matter cholesterol content has been observed in suicide individuals, particularly using violent methods (Lalovic et al., 2007). Together these data support a cholesterol-serotonin-impulsivity link that explains, in part, suicidal behavior.

It is possible that low peripheral cholesterol in psychiatric individuals accompanies (by a common regulatory mechanism) the cholesterol changes that may occur in specific synaptic lipid rafts, which could cause the hypoactivity of serotonergic communication and, in turn, lead to impulsivity and violent suicidal behavior. This is agreement with the idea that low cholesterol may act as a marker for central serotonergic activity (Kaplan et al., 1997; Vevera et al., 2005) and/or marker for suicidatility among depressive individuals (Lalovic et al., 2007). However, it is important to emphasize some limitations of the hypothesis of a common mechanism for the regulation of peripheral and synaptic lipid raft cholesterol content. Firstly, a common mechanism of regulation does not imply that the cholesterol content of these compartments are dependent upon each other, i.e. they are not necessarily communicable compartments. Secondly, the serum cholesterol is a well-determined compartment, but lipid rafts, even synaptic lipid rafts, are not well understood. It is possible that variations in cholesterol in specific brain regions, and cellular and subcellular concentration differences, exist. This aspect complicates our task of finding localized changes in lipid rafts and correlating them with suicidal behavior. Thirdly, brain cholesterol regulation is not limited to enzymes of synthesis, but also involves a complex protein machinery of secretion (in astrocytes), uptake (in neurons) and assembly in lipid rafts, which we need to understand much more.

In addition to serotonin hypofunction, at least 3 other mechanisms have been proposed to explain increased impulsivity in suicidal individuals: (1) serotonin–dopamine interaction, (2) steroid modulation of serotonin communication and (3) brain-derived neurotrophic factor (BDNF) decrease. However, it is possible that direct or indirect changes in lipid rafts may affect all these mechanisms. It has been suggested that serotonin depletion could be mediated by serotonin–dopamine interactions, in which a deficient inhibitory effect of serotonin on dopaminergic neurons would result in a higher dopamine activity (Harrison et al., 1997). It may be noted that D_1R dopamine receptors, in contrast to D_2R, are localized in lipid rafts and interact with Caveolin-1 (at least in the rat frontal cortex) (Voulalas et al., 2011), and that cholesterol changes could affect dopaminergic activity. Interestingly, cocaine leads to the migration of D_1R from lipid to non-raft fractions in rats (Voulalas et al., 2011), possibly explaining why cocaine use is associated with suicidal behavior (Vijayakumar et al., 2011). Moreover, dopamine transporters are also partially localized in lipid rafts and changes in cholesterol (depletion) content could modulate dopamine transport (decrease), consequently altering dopamine content (increase) in the synaptic cleft (Adkins et al., 2007).

An effect of steroid hormones on 5HT-mediated aggressive behavior has been reported; it is hypothesized that the interaction between low serotonin and high testosterone (an important extracerebral cholesterol-derivative) in the brain has a significant effect on the mechanisms of aggressive behavior (Birger et al., 2003). Corticosteroids may also play an important role in the relationship between stress, mood changes and, possibly, suicidal behavior by the downregulation of $5\text{-}HT_{1A}$ receptors (Pompili et al., 2010).

Decreases in BDNF (and cholesterol) contents have been associated with impaired brain plasticity among individuals with suicidal behavior (Lee and Kim, 2011). BDNF is a well-characterized modulator of synaptic plasticity and its signaling transduction depends on lipid raft integrity (Suzuki et al., 2004). Is important to mention that, in addition to the tight relationship between serotonin and BDNF (see Martinowich and Lu (2008) for a review), lipid rafts modulate BDNF activity, dependent on receptor tyrosine kinase B (TrkB) localized in these rafts; in turn, BDNF modulates lipid raft composition, stimulating the expression of cholesterol synthesis enzymes (Suzuki et al., 2007)

Taken together, data indicate the importance of brain cholesterol metabolism in the neurotransmission mediated by 5HT and its partners and modulators. However, it should be pointed out that many authors suggest that serotonergic hypofunction does not mediate violent behavior per se and that 5HT depletion should be considered a vulnerability factor for impulsive–aggressive behavior that may or may not be expressed depending on other biological factors, experience, and environmental support during development (Booij et al., 2010).

5. Are there other biochemical markers related to suicidal behavior and/or changes in cholesterol?

Serum cholesterol measurement is an important biological factor for the identification of individuals vulnerable to suicide but not, of course, when taken on its own. Other biological factors such as serum BDNF (Deveci et al., 2007), cerebrospinal fluid content of 5-hydroxyindolacetic (5HIAA, a serotonin metabolite) (Mann et al., 2006), prolactin response to fenfluramine (Corrêa et al., 2000), the dexamethasone suppression test (Coryell and

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Schlesser, 2001), and omega-3 and -6 polyunsaturated fatty acids (Garland et al., 2007) are taken into to consideration in this complicated task. All these biological factors, together with psychosocial factors, would allow the construction of a scale of the risk for suicide, as hypothetically proposed (Lee and Kim, 2011).

Serum S100B was recently proposed as a marker of suicidality in adolescents (Falcone et al., 2010). S100B protein is glial-derived protein and has been used as a general marker of brain injury (Gonçalves et al., 2008; Steiner et al., 2011). At least two mechanisms for increases in S100B, dependent on cholesterol, can be speculated. Firstly, a drop in cholesterol in the lipid raft may decrease $5HT_{1A}$ activity (which is negatively coupled to adenyl cyclase), which, in turn, could increase S100B secretion in astrocytes (Tramontina et al., 2008). Secondly, S100B plays a neurotrophic role that is meditated by RAGE (Donato et al., 2009), whose activity depends on the lipid raft content of cholesterol (Reddy et al., 2006). As such, cholesterol depletion would result in a lower activity of receptor (RAGE) and consequently (as compensation) higher levels of ligand (S100B) in the extracellular medium would be necessary. These possible links between extracellular increases in S100B and decreases in cholesterol in lipid rafts require further investigation. However, it is very important to emphasize that not only glial cells contribute to serum levels of S100B (Gonçalves et al., 2010). It is possible that changes observed in serum S100B in psychiatric patients may just reflect the altered adipose response of these patients (Steiner et al., 2010).

In support, other signals of altered adipose response in suicide attempters has been reported by the serum changes in two adipokines: leptin and ghrelin, which decrease and increase, respectively (Atmaca et al., 2006, 2008). In addition, changes in weight body and serum lipid levels induced by antiobesity drugs such as Rimonabant (Pi-Sunyer et al., 2006) also increased neuropsychiatric symptoms, including suicidal ideation (Nathan et al., 2011).

6. Conclusions

Suicide is a complex phenomenon involving biological and psychosocial factors. This review focused, herein, on one biological factor, cholesterol. In this review, we tried to establish a connection between the chain involving cholesterol, the lipid raft, and serotonin receptors with suicide. However, such associations require further evidence for their establishment, and currently we cannot support a causal association between low peripheral cholesterol and suicidal behavior in groups of psychiatric patients.

The general population does not demonstrate elements linking low peripheral cholesterol levels and suicidal behavior (e.g. Ellison and Morrison, 2001). Moreover, conflicting results of a relationship between cholesterol-lowering compounds and mood state are observed in the literature (While and Keen, 2012). In addition, it is still controversial as to whether the decrease in serum cholesterol induced by statins is accompanied by a decrease in the cholesterol of neuronal lipid rafts; for example platelet membranes do not demonstrate any decrease in lipid raft content (Vevera et al., 2005). As such, clinical and experimental data are necessary to support the possibility that low peripheral cholesterol may accompany specific changes in brain lipid rafts (assuming a common mechanism of regulation).

Although many neurochemical links for the cholesterol-serotonin-impulsivity hypothesis are lacking, it is possible that peripheral cholesterol and other related molecules (oxysterols, serotonin metabolites, S100B, BDNF) may be useful as markers for suicidal behavior. Moreover, it is necessary to take into account the substantial body of evidence of altered adipose response in these individuals, which may help us to understand suicidal behavior better and represents an additional instrument for the prevention of this painful behavior.

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Capítulo 02

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Research Report

Serum triglycerides, but not cholesterol or leptin, are decreased in suicide attempters with mood disorders

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ABSTRACT

Background: Many peripheral biomarkers, including low cholesterol and its fractions, have been examined to identify suicidal behavior. Herein, we assessed serum lipid profile and some proteins putatively associated with suicidal behavior in subjects with mood disorder (bipolar disorder or major depressive disorder) with a recent suicide attempt and with no lifetime history of suicide attempts.
Methods: Fifty subjects had presented an episode of attempted suicide during the last 15 days, and 36 subjects had no history of any suicide attempt. We measured total cholesterol, HDL, LDL and triglycerides as well as serum leptin, brain-derived neurotrophic factor (BDNF), S100B and C-reactive protein (CRP).
Results: Individuals that had attempted suicide presented decreased body mass index (BMI) and waist circumference. After adjusting for these confounders, we found that triglycerides were decreased in attempted suicide subjects. We found no differences among total cholesterol, LDL, and HDL or leptin, S100B, CRP and BDNF.
Limitations: This is a cross-sectional study, and we cannot therefore assess whether a decrease in triglycerides caused a mood episode with suicidal ideation that led to a suicide attempt or if the presence of a mood episode originated a loss of appetite and consequent loss of weight, therefore decreasing triglyceride levels.
Conclusions: These results do not support the hypothesis that lower levels of cholesterol are associated with suicidal behavior in a mood disorder sample. However, our data support the idea that adiposity is differentiated in these patients (reduced BMI, waist circumference and serum triglycerides), which could lead to an altered communication between the adipose tissue and brain.

1. Introduction

Suicide is a public health problem of high complexity, annually causing a premature loss of approximately one million lives worldwide (Bertolote and Fleischmann, 2002; Pompili et al., 2013), and generating a wave of psychic events in family, friends and society that are often irreparable. Many studies have searched for and proposed biological markers that might be linked to suicidal behavior and could be used as an additional tool for prevention and therapeutic actions (Arango et al., 2003; Asellus et al., 2010; De Luca et al., 2005; Lee and Kim, 2011; Marcinko et al., 2008; Pandey, 2013). Many peripheral markers have been investigated in persons vulnerable to suicide, including low serum cholesterol and its fractions (Atmaca et al., 2002; Chang et al., 2012; Coryell and Schlesser, 2007; Jee et al., 2011; Jokinen et al., 2010; Lee and Kim, 2003; Olie et al., 2011; Papadopoulou et al., 2013; Troisi, 2009). This is intriguing, considering that persons with mood disorders [particularly bipolar disorder (BD)] have an increased prevalence of metabolic syndrome, which includes obesity, increased waist circumference and hyperlipidemia (Fagiolini et al., 2005; Nousen et al., 2014; Vancampfort et al., 2013). However, the biochemical connection reported between obesity and suicidal behavior (Dutton et al., 2013; Mukamal and Miller, 2009) demands further characterization, not only with regard to the serum lipid profile, but in relation to proteins associated with adipose tissue, such as leptin (Eikelis et al., 2006).

The link between low cholesterol and suicidal behavior is not clear, but the association between cholesterol and mental illness has

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attracted the interest of researchers for over a century (Cruickshank and Tisdall, 1916; Poynder and Russell, 1926; Weston, 1915). Two meta-analyses summarize our current knowledge regarding cholesterol and suicidal behavior. Firstly, longitudinal studies show that individuals with lower cholesterol levels do have a slightly, but statistically significant, increased risk of completing suicide (Lester, 2002); secondly, cholesterol-lowering treatments, such as statins, have not been shown to increase non-illness mortality (including accidents, trauma and suicide) (Muldoon et al., 2001).

We analyzed the lipid profiles of subjects with mood disorders [BD and major depressive disorder (MDD)] and with a recent suicide attempt and in subjects with no lifetime history of suicide attempt. We aimed to determine whether total cholesterol, its fractions and triglycerides were decreased in subjects that had attempted suicide, as well as to investigate serum levels of other proteins putatively associated with suicidal behavior: leptin (Atmaca et al., 2008), S100B protein (Falcone et al., 2010), brain-derived neurotrophic factor (BDNF) (Pandey et al., 2010) and C-reactive protein (CRP) (De Berardis et al., 2008).

2. Methods and materials

2.1. Subjects and measurement

Eighty-six subjects with mood disorders (BD and MDD), according to DSM-IV criteria, were enrolled in the study upon admission to the São José Clinic, an inpatient psychiatric unit in Porto Alegre, Brazil, from April 2010 to December 2012. Of those, 50 had presented a suicide attempt during the last 15 days, and 36 had no lifetime history of suicide attempt. Suicide attempts were considered as "situations in which a person performs a life-threatening behavior with the intent of jeopardizing his or her life, or to give the appearance of such intent" (Beck et al., 1973; Brundin et al., 2007). All study participants underwent a general physical examination that showed no evidence of ongoing infection. Individuals on antibiotics and anti-inflammatory medications were excluded from the study. Demographic data and somatic diagnoses for the study participants are shown in Table 1. All subjects were on psychiatric medication for their current mood episode at the moment of sample collection. According to the criteria of Traskman et al. (1981), suicide attempters were further divided into two subgroups: 20 subjects with a violent attempt (5 subjects with a knife wound, 1 subject jumping from a high place, 1 with a firearm, 7 that had tried to hang themselves, and 6 that had thrown themselves in front of a vehicle in movement), and 30 with a non-violent attempt (medication ingestion and/or a superficial wrist cut). This study was approved by our local Ethical Review Board for human studies (UFRGS, 18153) in accordance with the 1964 Declaration of Helsinki. All subjects provided their written informed consent before being enrolled in this study.

2.2. Biochemical measurements

All subjects were fasted overnight. Venous blood samples were drawn from the antecubital vein at 08:00 a.m. After whole blood was obtained, the serum was separated by centrifugation at 3000 rpm for 15 min and was then aliquoted at −80 °C until analyses to determine the serum levels of cholesterol and triglycerides, as well as leptin, S100B protein, brain-derived neurotrophic factor (BDNF) and C-reactive protein (CRP).

Total cholesterol, HDL, LDL and triglyceride levels were determined by colorimetric assays using Labtest Diagnostica Kits, as indicated by the manufacturer, and employing the Labmax 240® equipment from Labtest Diagnóstica (Minas Gerais, Brazil). Serum S100B was measured by sandwich ELISA, as described previously (Leite et al., 2008). BDNF and leptin were measured by sandwich ELISA kits from Millipore (MA, USA). CRP was measured by a high sensitivity turbidimetric immunoassay kit from Biotécnica (Minas Gerais, Brazil), using the Labmax 240® for absorbance reading (Labtest Diagnostica, Minas Gerais, Brazil).

2.3. Statistical analysis

Statistical analyses were performed using SPSS 17.0 for Windows. All continuous variables are presented as means ± standard deviation (SD) or medians and interquartile range, as appropriate. Categorical variables are presented as the raw number and percentage (%). χ^2 and Fisher's test were used to evaluate associations between categorical variables, as appropriate. For the comparisons of continuous variables among groups, we employed the independent t test for parametric variables, and the Mann–Whitney test for non-parametric variables. For analyses of total cholesterol, LDL, HDL, triglycerides, BDNF, and leptin we used the analysis of covariance (ANCOVA). Length of illness and of current episode, sex, use of anticonvulsants or selective serotonin reuptake inhibitor (SSRI), body mass index (BMI), and waist circumference were used as covariates. As leptin was a highly skewed variable, we applied a logarithmic transformation in order to use parametric methods. S100 and CRP were highly skewed and not suitable for mathematical transformations, and therefore we used non-parametrical methods. Pearson's and Spearman's correlations coefficients were used to analyze the correlations between parametric and non-parametric continuous variables, respectively. We also analyzed the effect of the presence of suicide attempt as a moderator in the correlations. Two-tailed p values <0.05 were considered to be statistically significant.

3. Results

A total of 86 subjects with mood disorders were included in this study. Fifty subjects had presented an episode of suicide attempt during the last 15 days, and 36 subjects had no lifetime history of suicide attempt. The characteristics of the sample are summarized in Table 1. All subjects were on current psychiatric medication at the time of the suicide attempt and at the time of blood withdrawal. The frequencies of the types of psychiatric medication were similar between both groups, except for the use of anticonvulsants and SSRI antidepressants, which were higher in the subjects without any suicide attempt. Subjects with a recent suicide attempt had decreased BMI and waist circumference, when compared to subjects that had not attempted suicide. We identified the presence of T2DM (Type 2 diabetes mellitus) and hypothyroidism in subjects without any history of suicide attempt. After adjusting for length of illness and of current episode, sex, use of anticonvulsants and SSRI, BMI, and waist circumference, we found that triglycerides were decreased in attempted suicide subjects when compared to subjects without any suicide attempt (103.45 ± 31.72 vs. 144.15 ± 74.48, $p=0.001$) (Fig. 1). We found no differences among total cholesterol, LDL, and HDLbetween subjects with and without any suicide attempt.

Moreover, there were no differences among BDNF, S100B, CRP, and leptin between those attempted suicide and non-suicide subjects (Table 2). In addition, we found no difference in total cholesterol, LDL, HDL, triglycerides, BDNF, S100B, CRP, and leptin when analyzing the suicide attempters, according to the violence of the act (data not shown).

We found a positive correlation between leptin and length of illness ($r=0.24$, $p=0.03$), leptin and waist circumference ($r=0.32$, $p=0.003$), and between leptin and BMI ($r=0.48$, $p=0.001$). The correlation between leptin and BMI is clearly observed in subjects with and without suicide attempt (Fig. 2A). There were positive

Table 1
Characteristics of subjects with and without a history of suicide attempt.

Characteristic	With suicide attempt ($n=50$)	Without suicide attempt ($n=36$)	*P* value
Socio-demographics			
Male/female[a]	11/39	12/24	**0.048***
Age, years[b]	27.83 ± 12.21	32.28 ± 13.91	0.120
Education level, years[b]	10.27 ± 3.15	12.17 ± 3.09	0.064
Psychiatric disorder			
Pathology[a]			
Bipolar disorder	37	29	0.323
Current mania	23	16	0.658
Current depression	14	13	0.658
Major depressive disorder	13	7	0.323
Presence of psychosis[a]	21	8	0.133
Length of illness, years[c]	10.0 (3.0–20.0)	18.0 (11.0–30.0)	**0.032***
Length of current episode, days[c]	25.0 (15.0–60.0)	60.0 (30.0–180.0)	**0.046***
Family history of psychiatric disorder[a]	31	33	0.780
Current psychiatric medication[a]			
Antidepressants			
SSRI	7	14	**0.020***
Others	14	13	0.680
Lithium	15	11	0.570
Anticonvulsants	21	29	**0.021***
Antipsychotics			
Typical	28	17	0.280
Atypical	27	21	0.475
Metabolic characteristics			
BMI[b]	24.61 ± 4.77	28.13 ± 6.41	**0.001***
Waist circumference (cm)[b]	81.14 ± 9.48	96.68 ± 17.17	**0.049***
T2DM[d]	0	2	0.310
Hypothyroidism[d]	0	2	0.310

Abbreviations: SSRI, selective serotonin reuptake inhibitor; BMI, body-mass index; T2DM, Type 2 diabetes mellitus.

* Columns show means ± standard deviation (SD) for all categories except male sex, presence of psychosis, pathology, current psychiatric medication, family history of psychiatric disorder, and presence of T2DM or hypothyroidism, which are presented as raw data. Length of illness and current episode are shown as median and interquartile range.

[a] Chi-square test.
[b] Independent *t* test.
[c] Mann–Whitney test.
[d] Fisher's exact test.

correlations between CRP and waist circumference ($r_0=0.32$, $p=0.003$), and CRP and BMI ($r_0=0.38$, $p=0.001$). However, the presence of a suicide attempt did not act as a moderator in these correlations (Table 3). Moreover, we found no correlation between S100B and BDNF with any clinical characteristic, including BMI and length of illness.

With regard to the serum triglycerides (the parameter that differed between subjects with and without a history of suicide attempt) we found no correlations between triglycerides and BMI ($r=0.12$, $p=0.261$), triglycerides and waist circumference ($r=0.17$, $p=0.098$), or triglycerides and length of illness ($r=0.08$, $p=0.454$). The lack of correlation between triglycerides and BMI, observed in mood disorder subjects with and without a history of suicide, is shown in Fig. 2B.

4. Discussion

In contrast to current hypothesizes reported in the literature, we did not find any relationship between low total cholesterol and its fractions and suicidal behavior in patients with mood disorders. However, this lack of relationship is in agreement with some other studies in the literature (Almeida-Montes et al., 2000; Asellus et al., 2010; Paplos et al., 2012; Park et al., 2013; Persons et al., 2012) and our data are in accordance with two other independent and contemporary studies in individuals with BD and MDD, where no differences were found in serum cholesterol content (Baek et al., 2014; D'Ambrosio et al., 2012). We did not find any difference in total cholesterol, HDL or LDL. Commonly, psychiatric patients, particularly with BD and MDD, have elevated BMI and other metabolic abnormalities, which contribute to metabolic syndrome (Carpiniello et al., 2012; Fiedorowicz et al., 2008; Lopresti and Drummond, 2013). Herein, we found some differences between suicide attempters and non-attempters in the sample of mood disorders studied, particularly with regard to BMI and waist circumference, which were both reduced in suicide attempters. In agreement with these body parameters, the suicide attempters exhibited lower serum triglycerides. It is important to emphasize that the difference found in serum triglycerides (and not in cholesterol) in suicide attempters was adjusted for gender and BMI, which is generally underestimated in other cross-sectional studies of suicidality [see Zhang (2011)].

Three demographic data parameters deserve consideration in our sample; gender, length of illness and current episode and current medication. The gender difference regarding risk of suicide attempt is well known. Worldwide the risk of attempted suicide is higher in females (Borges et al., 2010; Rihmer et al., 2013). Accordingly, our study included more females than males with a history of attempted suicide. Furthermore, the average time between the onset of disease and the current suicide attempt was 10 years. This period has been considered to present a higher risk of suicide in patients with both BD and MDD (Tondo et al., 2003; Tsai et al., 2002). The use of SSRI and anticonvulsants was lower in suicide attempters. Atypical antipsychotics and anticonvulsants (particularly valproate) contribute to insulin resistance and obesity (Pylvanen et al., 2006; Verrotti et al., 2009). Notably, we did not find any differences in the use of antipsychotic drugs between suicide attempters and non-attempters. Triglyceride levels were decreased in subjects without suicide attempt even after adjusting for the use of anticonvulsants and SSRI. However, since ours is a cross-sectional study, we cannot

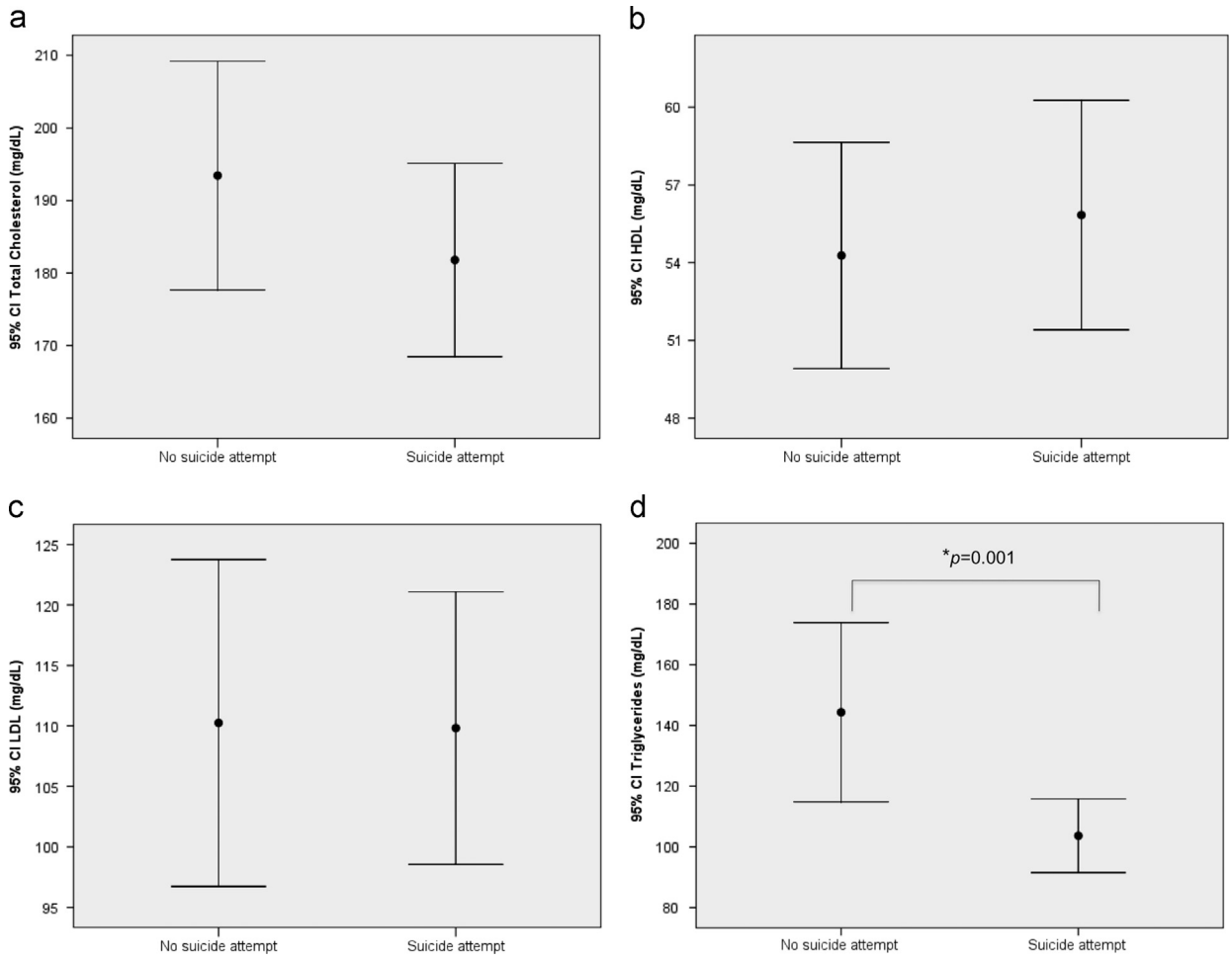

Fig. 1. Fasting serum lipid profile in subjects with and without a history of suicide attempt. (a) Total cholesterol, 181.00 ± 53.71 vs. 193.00 ± 44.70, respectively, $p=0.406$. (b) LDL cholesterol, 109.90 ± 44.97 vs. 111.55 ± 36.12, respectively, $p=0.504$. (c) HDL cholesterol, 54.50 ± 18.54 vs. 55.39 ± 13.13, $p=0.810$, and (d) Triglycerides, 103.45 ± 31.72 vs. 144.15 ± 74.48, $p=0.001$. Data are shown as mean ± standard deviation. Figure shows the mean and the 95% confidence interval (CI) of the mean. Analysis of covariance (ANCOVA) with length of illness and of current episode, sex, use of anticonvulsants and SSRI, BMI, and waist circumference as covariates.* denotes $p < 0.05$.

Table 2
BDNF, S100B, CRP, and leptin in subjects with and without a history of suicide attempt.

	With suicide attempt (*n*=50)	**Without suicide attempt (*n*=36)**	***P*** value
BDNF, pg/ml[a]	1070.94 ± 371.29	1045.38 ± 672.07	0.60
S100B, ng/ml[b]	3.00 (1.00–7.00)	3.50 (1.00–7.75)	0.85
CRP, mg/l[b]	4.00 (1.00–9.00)	3.50 (2.00–6.00)	0.89
Leptin, ng/ml[a,c]	2.74 ± 1.12	3.05 ± 1.19	0.65

Abbreviations: BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein.
[a] Independent *t* test, mean and standard deviation.
[b] Mann–Whitney test, median and interquartile range.
[c] Log-transformed variable.

rule out that the use of anticonvulsant drugs, which were more prevalent in the non-attempter group, contributed to the discrepancy observed in BMI and serum triglyceride levels. In another study regarding BD, decreased cholesterol and triglycerides were observed in suicide attempters (Vuksan-Cusa et al., 2009). Interestingly, in Vuksan-Cusa's study the sample was free of psychotropic medication, reinforcing the idea that medication is not the sole contributor to changes in lipid profile.

It has been proposed that a decreased serotonergic activity could result in a poorer inhibition of impulsivity and, consequently, suicidal behavior (Arango et al., 2002; Mann, 2013). In our study, we observed that the prescription of SSRI in persons without suicide attempts was higher than in those with suicide attempts. This difference in prescribing may be secondary to a possible association between the class of SSRI, particularly fluoxetine, with violence and suicide (Gunnell and Ashby, 2004; Hammad et al., 2006; Marcinko, 2007; Walsh and Dinan, 2001), although no consensus regarding the direct relationship between antidepressant use and development of suicidal ideation or behavior exists (Fazel et al., 2007; Hammad et al., 2006; Miller et al., 2014; Walsh and Dinan, 2001). More recently, the serotonergic system, widely established as being linked to suicidality (Arango et al., 1995; Jokinen et al., 2009; Traskman et al., 1981), has been studied in the area of genetics and presented interesting results. For example, the presence of sequence variants in HTR5A (serotonin type 5A receptor gene) was strongly associated with high plasma levels of triglycerides (Zhang et al., 2010) and associations between lower HDL cholesterol levels with depression were also modified by a 5-HTTLPR (serotonin transporter gene linked promoter region) polymorphism; however this association was only significant in the presence of one or more copies of the s (short) allele (Kim et al., 2011).

Some studies have suggested that lower cholesterol can be more linked to violent suicide attempts than suicidality itself [e.g. (Atmaca et al., 2008)]. We did not find a significant difference in

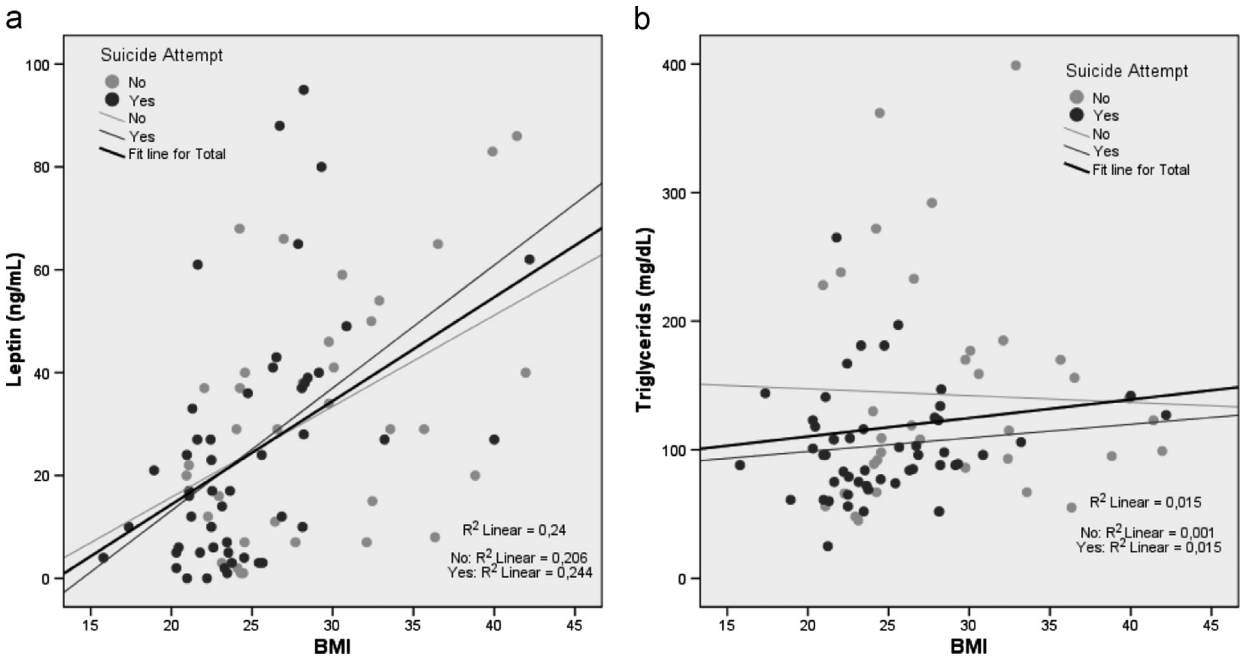

Fig. 2. Correlations between leptin or triglycerides with body-mass index (BMI). A positive correlation between leptin and BMI is observed (in a, $r=0.48$), but no correlation between triglycerides and BMI (in b, $r=0.12$). History of suicide attempt is not a moderator of the correlations ($p>0.05$).

Table 3
Analysis of a "history of suicide attempt" as a moderator of the correlations between body-mass index and length of illness in years with C-reactive protein, leptin, brain-derived neuotrophic factor (BDNF), protein S100B, and lipidic profile.

	R* values with suicide attempt ($n=50$)	***R* values without suicide attempt ($n=36$)***	***P*** value
BMI vs. BDNF	0.17	−0.15	0.472
BMI vs. CRP	0.38	0.45	0.563
BMI vs. Leptin	0.45	0.39	0.555
BMI vs. S100B	0.08	−0.05	0.549
Length of illness vs. BDNF	−0.26	−0.06	0.289
Length of illness vs. CRP	0.01	0.15	0.782
Length of illness vs. Leptin	0.19	0.25	0.878
Length of illness vs. S100B	0.16	−0.06	0.281

* Columns show Pearson's correlation (r). The P values refers to the effect of the presence of suicide attempt as a moderator to the correlations.

serum cholesterol between violent and non-violent attempters, in agreement with a previous study in BD (D'Ambrosio et al., 2012). We also did not find any difference in triglyceride levels between violent and non-violent suicide attempters.

This study also evaluated other markers related to adiposity, namely leptin, CRP and S100B (Eikelis et al., 2006; Steiner et al., 2010a). BDNF was also investigated because it is widely involved in body energetic homeostasis and commonly associated with psychiatric disorders with an elevated rate of suicide (Fernandes et al., 2013, 2011; Marosi and Mattson, 2014).

Serum leptin, an adipocyte-derived protein regulator of food intake, has a positive correlation with BMI [e.g. (McConway et al., 2000)]. Leptin (together with cholesterol) was found to be reduced in suicidal patients, compared to healthy controls (Atmaca et al., 2008, 2002). In addition, low levels of cerebrospinal leptin were found in female suicide attempters with major depression (Westling et al., 2004), in agreement with reduced levels of brain leptin observed in suicide victims (Eikelis et al., 2006). However, serum leptin was not altered in pregnant women with a higher suicide risk (Farias et al., 2013). Herein, we found a positive correlation of leptin with BMI in our sample, but no difference was found in serum leptin between patients with and without a history of suicide. This finding contends the idea that serum leptin may act as a suicidality marker in patients with mood disorders. Moreover, we did not find an association between CRP and a history of suicide in patients with mood disorders. However, the positive correlation between CRP and BMI and CRP and waist circumference in these patients reinforces the idea that a systemic inflammatory process (including adipose tissue) may contribute to the pathophysiology of mood disorders (Kling et al., 2007).

No differences were observed in serum BDNF and S100B between mood disorder subjects with and without a history of suicide. Moreover, no correlation was found between these proteins and the anthropomorphic signals of adiposity observed in these patients (BMI or waist circumference) or these proteins and the length of illness. Serum BDNF was reduced in suicidal individuals soon after an attempted suicide (Dawood et al., 2007), in agreement with the changes in brain BDNF and its receptors observed in postmortem studies of depressive patients (Lee and Kim, 2011). Our sample included patients with suicide attempts during the last 15 days, time enough to "recover" possible decreases in the peripheral levels of BDNF associated with a suicidal attempt. However, further studies are necessary to clarify this question. S100B increments have been reported in many conditions of brain injury and neurodegenerative diseases (Kleindienst et al., 2007; Rothermundt et al., 2003). Serum S100B protein comes from the brain and from other non-neural sources, particularly adipose tissue (Goncalves et al., 2010, 2008). In fact, serum S100B levels in humans appear to closely reflect adipose tissue mass (Gross et al., 2010; Steiner et al., 2010a). Some studies have shown elevated levels of serum S100B in episodes of mood disorders, and these elevations were more evident in major depressive disorder than in bipolar disorder (Schroeter and Steiner, 2009). We found elevated levels of S100B (compared to those of healthy individuals) [e.g. (Andreazza et al., 2007; Schroeter et al., 2011)], but no difference was found between patients with and without a

history of suicide attempt. Moreover, no correlation was found with BMI. Interestingly, this lack of correlation was also observed in schizophrenic patients and attributed to insulin resistance in these patients (Steiner et al., 2010b). However, augmented S100B was correlated with the severity of suicidal ideation in adolescents with psychosis or mood disorders (Falcone et al., 2010). As such, this matter demands further studies.

Our study presents some limitations; firstly, our sample is probably underpowered to detect a difference in total cholesterol between subjects with and without a history of suicide attempt. However, in support of our analysis, another cross-sectional study of a sample of schizophrenic patients, also adjusted for gender and BMI, found no association between cholesterol and suicidal behavior (Huang and Wu, 2000). Secondly, all subjects were on medication and a higher number of non-suicidal persons were on anticonvulsants, drugs known to increase insulin resistance; however, we adjusted for this type of medication in our analysis. Thirdly, ours was a cross-sectional study, and we cannot therefore assess whether a decrease in triglycerides caused a mood episode with suicidal ideation that led to a suicide attempt or if the presence of a mood episode originated a loss of appetite and consequent loss of weight, therefore decreasing triglyceride levels.

Taken together our data suggest that suicide attempters with mood disorders exhibit less adiposity, expressed as a reduced BMI, waist circumference and serum triglycerides, when compared to non-attempters. Our data opposed the idea that serum leptin, CRP and S100B could represent the markers of suicidality in patient with mood disorders. However, further studies are investigating these and other markers related to adiposity, such as ghrelin (Atmaca et al., 2006), are necessary not only to diagnose such behavior, but for the follow-up of treatment of psychiatric diseases with elevated rates of suicide.

5. Conclusions

We did not find any decrease in serum cholesterol when comparing suicide attempters with non-attempters in a sample of subjects with mood disorders. However, we found a reduced adiposity in suicide attempters, as indicated by reduced BMI, waist circumference, and peripheral triglycerides. These data do not support the hypothesis that lower levels of cholesterol are associated with suicidal behavior. Moreover, although peripheral levels of leptin, BDNF, S100B and CRP may be associated with mood disorders, we did not find any difference in the levels of these proteins in subjects that had a history of suicide, or not. However, our data contribute to the idea that adiposity is differentiated in these patients, which could lead to an altered adipose tissue–brain communication.

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Conflict of interest

The authors declare no conflict of interest.

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4. DISCUSSÃO

O comportamento suicida é um fenômeno de elevada complexidade. Seja descrito nas artes, imortalizando autores e personagens, ou foco de estudo nas diversas áreas do conhecimento, o suicídio é apresentado como resultado de uma larga rede de fatores que confluem e se materializam em dado momento e sob determinadas condições. É possível dizer que o diagnóstico de risco de suicídio durante uma avaliação psiquiátrica está baseado em dados subjetivos, embora absolutamente necessários.

Se por um lado o conhecimento dos fatores associados ao comportamento suicida é um valioso instrumento para sua prevenção, por outro lado fatores de risco clínicos têm baixo poder preditivo e não fornecem a segurança desejada para identificar a propensão individual e existência ou não de risco iminente para que medidas específicas sejam tomadas e plenamente justificadas, como internação hospitalar imediata, supervisão constante, intervenção farmacológica, terapia eletroconvulsiva e condutas a serem tomadas no tratamento e seguimento em longo prazo.

A possibilidade de utilização de biomarcadores na área psiquiátrica certamente já retrata o avanço científico adquirido em uma área da medicina carente de métodos objetivos de avaliação. Importante fonte de informações para pesquisas nesta área, o sistema serotoninérgico tem sido amplamente estudado e fortemente relacionado a neurobiologia do comportamento suicida, (ANGUELOVA et al., 2003; LI e HE, 2007; SHER et al., 2007; SADKOWSKI et al., 2013; COSTANZA et al., 2014), principalmente após achados de concentrações significativamente menores do metabólito da 5-hidroxitriptamina (5-HT/serotonina), o ácido 5-Hidroxiindolacético (5-HIAA), no líquido cefalorraquidiano de pacientes com tentativa de suicídio em relação aos controles e particularmente naqueles com tentativas consideradas violentas (ASBERG et al., 1976; TRÄSKMAN et al., 1981). Outras relações têm sido

encontradas em sistemas de neurotransmissão como o sistema dopaminérgico (ROY et al., 1989; SHER et al., 2006), noradrenérgico (KAMALI et al., 2001; SUBLETTE et al., 2006), endocanabinóide (VINOD e HUNGUND, 2006) e metabolismo lipídico (DE BERARDIS et al., 2009).

Os resultados aqui discutidos são decorrentes de um estudo que incluiu 86 pacientes com desordem do humor - 36 sem história de tentativa de suicídio, em qualquer período da vida, e 50 que haviam apresentado no mínimo uma tentativa de suicídio no período de quinze dias, espaço de tempo no qual os pacientes foram entrevistados, obtidos os dados referentes ao peso, altura e circunferência da cintura (CC) e foi realizada a coleta de sangue para análise e determinação dos níveis séricos de colesterol total e frações, triglicerídeos, leptina, S100B, BDNF e PCR.

Características Sociodemográficas

- Sexo

Estudos sobre o comportamento suicida têm mostrado diferenças entre os sexos, mulheres apresentando maior risco para tentativa de suicídio enquanto homens evidenciam taxas mais elevadas de morte por suicídio (HAWTON, 2000; SCHRIJVERS et al., 2012). Em correspondência com a literatura, 39 (78%) dos 50 indivíduos com tentativa de suicídio incluídos em nossa pesquisa eram do sexo feminino. Uma inversão deste quadro foi relatada na zona rural da China, onde o número de mulheres jovens que morrem por suicídio tem superado os óbitos entre homens pela mesma causa (CHEN et al., 2012).

O fato de que mais homens alcançam sucesso no ato suicida tem sido relacionado à escolha de métodos mais violentos - enforcamento, arma de fogo e lançar-se de lugares elevados, como pontes e viadutos - enquanto mulheres escolhem, com

maior frequência, métodos considerados não violentos, como ingestão de medicamentos, permitindo chegada a tempo de socorro (MURPHY, 1998; NOCK e KESSLER, 2006). Outros fatores relacionados com a maior taxa de morte entre homens seriam a elevada prevalência de dependência ao álcool e outras substâncias e menos frequentemente irem a tratamento por depressão (SKOGMAN, 2004). É de fundamental importância não menosprezarmos as tentativas de suicídio em mulheres ou as tentativas de suicídio por si só, como se representassem menor risco, utilizando uma visão ultrapassada de "quem tenta não faz" ou de forma mais pejorativa "cão que ladra não morde". Portanto, é válido considerar que tentativa de suicídio prévia é um dos mais fortes fatores preditivos de novas tentativas e que elevação da frequência favorece o sucesso em algum momento (SKOGMAN, 2004). Um estudo que acompanhou por dois anos pacientes com diagnóstico de depressão maior e desordem bipolar mostrou aumento em mais de 30 % no risco de nova tentativa a cada tentativa anterior (OQUENDO et al., 2007). Em outro, com acompanhamento de 14 anos, os autores encontraram permanência do risco após tentativa para ambos os sexos, sendo que mulheres apresentaram menor relação com o tempo e homens demonstraram prognóstico menos favorável dentro do primeiro ano após a tentativa (SUOKAS et al., 2001).

Diferenças no sistema serotoninérgico entre sexos já foi descrito em animais, com níveis mais elevados de serotonina em SNC e de 5-HIAA em líquor de ratos fêmeas quando comparados a machos (ROSECRANS, 1970), e em exames *post mortem* em humanos (GOTTFRIES et al., 1974). Recentemente, através de exames in vivo utilizando Tomografia por Emissão de Pósitrons (PET) com voluntários saudáveis, os autores encontraram diferenças na neurotransmissão serotoninérgica entre homens e mulheres. Elas apresentaram maior densidade de receptor 5-HT_{1A} e menor densidade de

5-HTT (JOVANOVIC et al., 2008). Estes achados nos aproximam ainda mais de uma participação biológica para as diferenças entre sexos encontradas na epidemiologia do comportamento suicida e outros transtornos mentais como os que envolvem ansiedade (PIGOTT, 1999) e depressão (KESSLER et al., 1993).

- Idade

Não encontramos diferença estatisticamente significativa entre os grupos em relação a média de idade dos indivíduos com e sem tentativa de suicídio, respectivamente 27.83±12.21 e 32.28±13.91 (ver tabela 1, no segundo artigo). Cabe observar que não houve imposição de limite de idade para a inclusão em nosso estudo e que a média de idade encontrada na amostra pode ser um reflexo das características do local no qual a pesquisa foi desenvolvida. Apesar de não aparecerem em nossa amostra, indivíduos idosos continuam representando um grupo de elevado risco para suicídio, principalmente do sexo masculino (VIDAL et al., 2013). No Brasil, em 2009, as mortes por causa externa ocuparam o sétimo lugar entre pessoas com 60 anos ou mais, foram 21.437 vítimas, 1.378 óbitos foram registrados como suicídio e em 3.364 casos não foi possível distinguir entre acidente, lesão autoinfligida ou agressão (PINTO et al., 2012). Considerando dados referentes a população idosa na Europa Ocidental o número de suicídios consumados crescem enquanto diminuem as tentativas de suicídio (DE LEO et al., 2001). Em adição, tanto a literatura nacional quanto internacional tem registrado aumento do comportamento suicida na população mais jovem nos últimos anos (MENEGHEL et al., 2004; LOVISI et al., 2009).

- Índice de Massa Corporal (IMC) e Circunferência da Cintura (CC)

A utilização de índices antropométricos para avaliação de obesidade, como o índice de massa corporal (IMC), a relação cintura-quadril (RCQ) ou somente a circunferência da cintura (CC) e as dobras cutâneas (DC), tem sido recomendada pela

simplicidade de execução e baixo custo financeiro (WORLD HEALTH ORGANIZATION - WHO, 1997).

Nossa pesquisa incluiu o cálculo do IMC e medida da CC. O primeiro é o resultado do peso de uma pessoa (em quilogramas) dividido pelo quadrado de sua altura (em metros) e está fortemente relacionado com a massa de gordura absoluta, é um método amplamente difundido, com aplicação tanto na clínica quanto em pesquisa para determinação da existência e grau de obesidade (KLINITZKE et al., 2013). A circunferência da cintura foi medida seguindo os critérios da OMS, a saber, posicionando a fita métrica em torno do tronco, paralela ao chão, passando por um ponto a meio caminho entre o bordo inferior da última costela palpável e a parte superior da crista ilíaca, ao final da expiração (WHO, 2008). Assim, a escolha da medida do IMC teve por objetivo avaliação da adiposidade geral enquanto a determinação da CC permitiu por meio indireto acessar a gordura intra-abdominal (visceral ou central) (LEAN et al., 1995).

Há um consenso de que pessoas obesas possuem alto risco de desenvolverem doença cardiovascular aterosclerótica, certas neoplasias, hipertensão arterial sistêmica, diabetes mellitus tipo 2, hipertrigliceridemia, baixos níveis de colesterol HDL, esteatose hepática e evoluírem para mortalidade precoce (KRAUSS e WINSTON, 1998; GARG e MISRA, 2002; GARG, 2004), situações clínicas que também são frequentes em pacientes com transtornos mentais (HERBST et al., 2007; MITCHELL et al., 2011; STANLEY e LAUGHARNE, 2012). Por outro lado, alguns autores acreditam que a relação entre o IMC e risco aumentado de determinadas patologias pode ser influenciada pela distribuição de gordura, onde o acúmulo em abdômen está vinculado às consequências da obesidade, independente do peso corpóreo (DESPRÉS et al., 1985; POULIOT et al., 1994; TAYLOR et al., 1998). A participação da obesidade no

desenvolvimento da doença cardíaca coronariana é amplamente aceita, mas seu papel exato e mecanismos subjacentes aguardam a continuidade das pesquisas, há indícios de que possa a obesidade ser um fator de risco independente (HUBERT et al., 1983). A mesma discussão pode ser feita quanto ao papel da obesidade na doença mental e, mais especificamente, dos depósitos de gordura intra-abdominal (HO et al., 2008; RIVENES et al., 2009).

A esta já intrincada rede de fatores agregam-se pesquisas que tem demonstrado uma inter-relação entre IMC e transtornos mentais, incluindo suicídio, possibilidade que deve ser analisada em relação a adiposidade e uma possível vinculação a comportamento suicida.

Há muito tempo depressão e obesidade tem sido vistos como interligados, muitas vezes sendo a baixa autoestima, decorrente da imagem corporal indesejada, a justificativa que torna compreensível esta suposta relação. No entanto, estudos com indivíduos obesos e não obesos não são unânimes quanto a uma relação positiva entre obesidade e desordem mental. Obesidade foi relacionada a baixos níveis de ansiedade (SEGERS e MERTENS, 1974; CRISP e MCGUINESS, 1976; STEWART e BROOK, 1983), a menor índice de depressão (SEGERS e MERTENS, 1974; STEWART e BROOK, 1983) e uma associação com baixos níveis de depressão em homens (CRISP e MCGUINESS, 1976). Por outro lado, obesidade foi associada à depressão (ROBERTS et al., 2002; FAITH et al., 2002; HEO et al., 2006) e algumas pesquisas mostram uma relação com depressão em mulheres (CARPENTER et al., 2000; SCOTT et al., 2008a; SCOTT et al., 2008b).

Pelo menos há cinquenta anos o IMC tem sido avaliado em estudos que envolvem o tema suicídio, como o realizado com estudantes universitários onde o peso ajustado para a altura mostrou-se menor naqueles que posteriormente cometeram

suicídio em relação aos controles (PAFFENBARGER e ASNES, 1966). Atualmente um conjunto de evidências tem surgido relacionando inversamente o IMC, então como medida de adiposidade geral, e risco de morte por suicídio, como demonstrado em importantes estudos (CARPENTER et al., 2000; MAGNUSSON et al., 2006; ZHANG, 2006; MUKAMAL et al., 2007; KAPLAN et al., 2007; BJERKESET et al., 2008; MUKAMAL et al., 2010). Em nossa pesquisa pacientes com TS apresentaram IMC e CC diminuídos quando comparados aos demais pacientes**.** Cabe salientar que os indivíduos incluídos nesta pesquisa não realizavam atividade física de forma regular e aqueles com TS não sofreram perdas físicas que comprometessem o peso corporal em relação ao IMC.

Foi proposto que o tecido adiposo visceral tem um importante papel no desenvolvimento de resistência a insulina e outras complicações metabólicas (BAPTISTA et al., 2015). Como dito anteriormente, os pacientes com TS também apresentaram CC reduzida em relação aos sem TS.

- Transtorno Psiquiátrico, Tempo de Doença e Psicofármacos

A amostra deste trabalho foi constituída por pacientes que fecharam critérios pelo DSM-IV para Desordem Bipolar (episódio atual maníaco ou depressivo) e Desordem Depressiva Maior. Entre os grupos de pacientes com e sem tentativa de suicídio não houve diferença em relação ao diagnóstico e nem ao tipo de episódio atual. Muitas pesquisas têm contribuído para a melhor compreensão das patologias mentais, mas a causa precisa, ou o fator determinante, ainda não são conhecidos. Dados evidenciam que a existência destes distúrbios está entre os principais fatores de risco para o comportamento suicida, uma sobreposição mesmo que parcial sugere a existência de mecanismos inter-relacionados, tornando válida e imprescindível toda informação adquirida para esta área. Através da chamada autópsia psicológica é possível identificar

e reconstruir características do indivíduo que morreu por suicídio, para isto é utilizada toda informação que possa ser recuperada através de prontuário hospitalar, registros médicos e entrevistas com pessoas próximas (HAWTON et al., 1998). Utilizando desta ferramenta, pesquisadores identificaram a presença de uma ou mais desordens mentais em 90% daqueles que se mataram (CAVANAGH et al., 2003; NOCK et al., 2009).

Ainda sobre suicídio, metade a dois terços sofriam com desordem de humor (CAVANAGH et al., 2003; ARSENAULT-LAPIERRE et al., 2004). Em adição, risco de TS e de suicídio parece ser discretamente maior naqueles com desordem bipolar, embora não pareça haver diferença entre TS durante os episódios depressivos dos diferentes tipos de desordem do humor (PANDEY, 2013; ISOMETSÄ, 2014). Estas importantes informações justificam investimento humano e material para a continuidade das pesquisas sobre comportamento suicida e desordens de humor. Por outro lado, ainda não há resposta que explique porque nem todos os pacientes com transtornos de humor se suicidam ou tentam o suicídio, mas certamente indicam que outros fatores de risco estão presentes na instalação da ideação suicida até sua evolução para o óbito. Estudos têm reforçado a ideia de que uma predisposição genética ao comportamento suicida possa ser um fator de risco independente da desordem psiquiátrica presente, ao menos de forma parcial (OGDEN et al., 2004; PANDEY, 2013).

Outro aspecto importante foi o tempo médio de 10 anos entre o início da doença e a TS atual, período este que tem sido considerado como de maior risco para suicídio tanto em pacientes com desordem bipolar quanto com diagnóstico de desordem depressiva do humor (TSAI et al., 2002; TONDO et al., 2003).

Outro aspecto que merece consideração é a medicação usada em nossa amostra, particularmente no que se refere a anticonvulsivantes e ISRSs (antidepressivos inibidores seletivos da recaptação de serotonina). A prescrição destas duas classes

farmacológicas foi menor no grupo de pacientes com TS (grupo que também apresentou parâmetros menores de IMC e CC); por outro lado, não houve diferença no uso de antipsicóticos nem de lítio entre os indivíduos que tentaram e aqueles que não tentaram suicídio. Anticonvulsivantes, lítio e antipsicóticos atípicos podem contribuir para obesidade e resistência à insulina (MCINTYRE et al., 2003; PYLVÄNEN et al., 2006; VERROTTI et al., 2009). Desta forma, sendo um estudo transversal, não podemos descartar que o uso de anticonvulsivantes tenha colaborado para as diferenças encontradas no IMC e níveis séricos de triglicerídeos, considerando que a prevalência de seu uso foi maior em não tentadores de suicídio. Outro estudo, desta vez com indivíduos bipolares mas sem uso de medicação, também demonstrou níveis menores de triglicerídeos em pacientes com tentativa de suicídio (o mesmo acontecendo com o colesterol) (VUKSAN-CUSA et al., 2009), contribuindo para a ideia de que as alterações no perfil lipídico não resultaram somente do efeito do uso de anticonvulsivantes.

- Colesterol total, HDL e LDL

Apesar dos inúmeros trabalhos demonstrando a relação dos níveis baixos de colesterol periférico com comportamento suicida (SCHUIT et al., 1993; ZUREIK et al., 1996; BOCCHETTA et al., 2001; KIM e MYINT, 2004; CORYELL e SCHLESSER, 2007; CHANG et al., 2012; PAPADOPOULOU et al., 2013), particularmente com tentativas violentas e associação com impulsividade (VEVERA et al., 2003; ALVAREZ et al., 2000; KIM et al., 2002; ATMACA et al., 2008), nossa pesquisa não evidenciou diferença nos níveis de colesterol total e suas frações entre indivíduos com ou sem tentativa de suicídio. Discrepância devido ao IMC podem ter gerado estas diferenças, já que outro estudo (transversal e com pacientes esquizofrênicos), também ajustado para sexo e IMC, também não encontrou associação entre colesterol e

comportamento suicida (HUANG e WU, 2000). Nossos resultados estão de acordo com outros trabalhos mais recentes (ALMEIDA-MONTES et al., 2000; DEISENHAMMER et al., 2004; D'AMBROSIO et al., 2012; PARK et al., 2014**).**

Em artigo publicado recentemente, resultante dos estudos realizados durante esta pesquisa, estão disponíveis informações complementares sobre a possível ligação entre o colesterol e comportamento suicida, associação esta que não encontramos no grupo de pacientes estudados (CANTARELLI et al., 2014).

- Outros marcadores: Leptina, PCR, S100B e BDNF

Também não encontramos diferença nos níveis séricos de leptina, proteina C reativa (PCR), S100B e BDNF entre os pacientes com e sem tentativa de suicídio, ou mesmo com o perfil de violência do ato.

A leptina tem sido apontada como possível marcadora nos casos de suicídio (ATMACA et al., 2002; EIKELIS et al., 2006; ATMACA et al., 2008; AUWERTX e STAELS, 1998). No entanto, não houve diferença em nossa amostra ($p = 0.65$). Por outro lado, a análise dos dados demonstrou uma correlação positiva entre leptina e duração da doença ($r = 0.24$, $p = 0.03$), leptina e CC ($r = 0.32$, $p = 0.003$) e particularmente entre leptina e IMC ($r = 0.48$, $p = 0.001$).

A PCR foi apontada como alterada em pacientes suicidas (O'DONOVAN et al., 2013; SUCHANKOVA et al., 2013). Neste trabalho achamos uma correlação positiva entre PCR e CC ($r_0 = 0.32$, $p = 0.003$) e PCR e IMC ($r_0 = 0.38$, $p = 0.001$), mas nenhuma com o comportamento suicida. A correlação positiva encontrada em nosso trabalho entre PCR / IMC e PCR / CC reforça a ideia de que um processo inflamatório sistêmico está presente e provavelmente contribuindo para a fisiopatologia das desordens do humor e comportamento suicida.

A S100B foi descrita como um possível marcador para risco de suicídio em pacientes adolescentes com diagnóstico de esquizofrenia ou desordem de humor (FALCONE et al., 2010). Não observamos alteração em nossa amostra, o que poderia ser atribuído a faixa etária ou ao tipo de desordem analisada.

O BDNF é a neurotrofina mais abundante no SNC, mas também abundante na periferia, sendo capaz de atravessar a BHE (barreira hematoencefálica) em ambas as direções (CHO et al., 2012) e pode ser medido tanto no soro quanto no plasma humano (FUJIMURA et al., 2002; RADKA et al., 1996). Segundo Rosenfeld et al., 1995, níveis séricos podem superar até duzentas vezes os valores plasmáticos (ROSENFELD et al., 1995). A origem do BDNF não é clara, além do encéfalo, diferentes epitélios, células brancas e plaquetas são outras fontes conhecidas (ROSENFELD et al., 1995; FUJIMURA et al., 2002; PLIEGO-RIVERO et al., 1997; TÜRCK e FRIZZO, 2015). Um estudo com pacientes com desordem depressiva de humor e livre de medicação, encontrou tanto em soro quanto em plasma níveis de BDNF reduzidos em relação a controles normais, porém a dosagem feita em sangue total destes pacientes foi inalterada em relação aos controles (KAREGE et al., 2005). Poro outro lado, pesquisas têm demonstrado aumento dos níveis séricos de BDNF em resposta ao uso de medicações psicotrópicas como antidepressivos (DWIVEDI, 2012) e antipsicóticos atípicos, particularmente olanzapina (GONZÁLEZ-PINTO et al., 2010). Assim, muitos fatores podem interferir na interpretação dos resultados referentes a dosagem de BDNF circulante.

- Triglicerídeos

Poucas estudos tem avaliado a associação entre níveis séricos de triglicerídeos e comportamento suicida (RYBAKOWSKI et al., 1996; SEEFRIED e GUMPEL, 1997; LEE e KIM, 2003; VUKSAN-CUSA et al., 2009; D'AMBROSIO et al., 2012), porém

em 2014, pelo menos, quatro estudos foram publicados, incluindo uma das publicações resultantes deste trabalho (BAEK et al., 2014; AINIYET e RYBAKOWSKI, 2014; PARK et al., 2014; CANTARELLI et al., 2015).

Assim como o colesterol, os triglicerídeos são lipídeos, porém formados a partir do glicerol e ácidos graxos. Enquanto em nossa pesquisa não encontramos nenhuma diferença entre colesterol total, LDL e HDL entre pacientes com e sem TS, ajustando para tempo de doença e episódio corrente, sexo, uso de anticonvulsivante e ISRS, IMC e CC, os níveis de triglicerídeos estavam reduzidos naqueles com TS em relação aos sujeitos sem história de TS. Achado similar foi encontrado por Park et al., 2014, onde pacientes deprimidos com ideação suicida apresentaram triglicerídeos reduzidos em relação aos controles também deprimidos mas sem ideação suicida; interessante que assim como em nossa pesquisa, também não foi encontrado correlação entre triglicerídeos e IMC. Baek et al. (2014), também encontraram associação de triglicerídeos reduzidos com TS recente em pacientes com depressão enquanto Ainiyet e Rybakowski (2014), obtiveram o mesmo resultado avaliando pacientes com esquizofrenia.

O sistema serotoninérgico tem sido amplamente pesquisado e associado ao comportamento suicida, como correlação inversa entre níveis de 5-HIAA em LCR e risco de suicídio em deprimidos, aumento da densidade em sítios de ligação de serotonina em córtex frontal de vítimas de suicídio, redução da resposta da prolactina a administração de fenfluramina e uma quantidade de outros achados que colocaram o sistema serotoninérgico como um sistema chave na fisiopatologia do comportamento suicida (KLEMPAN e TURECKI, 2005). Com o desenvolvimento já alcançado na área da genética, avanços estão sendo estendidos para a área médica da psiquiatria. Mais recentemente, a presença da sequência variante de HTR5A (*serotonin type 5A receptor*

gene) foi fortemente associado a níveis plasmáticos elevados de triglicerídeos (ZHANG et al., 2010). Segundo os dados disponíveis em Ogden et al (2004), seis dos genes candidatos NPY2R (*neuropeptide Y receptor 2*), 5HTR2C (serotonin receptor 2C), CCK, BDNF, GNAI2 (G protein alpha-inhibiting activity polypeptide 2) e PTEN (*phosphatase and tensin homologue*) estão relacionados a desordem de humor em modelos animais e em estudos *postmortem* de suicidas, em adição, no mínimo cinco deles, a saber, NPY2R, 5HTR2C, CCK, BDNF e PTEN modulam a ingestão alimentar e podem estar envolvidos na obesidade (OGDEN et al., 2004; BRUMMETT et al., 2008). Portanto, novos achados reforçam que seja perfeitamente possível que o metabolismo lipídico esteja implicado na fisiopatologia das desordens mentais e, mais especificamente, no comportamento suicida.

Níveis séricos aumentados de triglicerídeos foram relacionados a melhor desempenho cognitivo em pacientes idosos (YIN et al., 2012). Por outro lado, o comportamento suicida parece ser acompanhado por comprometimento cognitivo (AYALON e LITWIN, 2009; LARA et al., 2014), embora os pacientes que participaram deste estudo não passaram por testes de avaliação cognitiva, fica aqui a especulação se a redução de triglicerídeos foi acompanhada de mudanças cognitivas.

2. CONCLUSÕES

Os resultados desta pesquisa foram compatíveis com a hipótese de relação entre adiposidade e tentativa de suicídio em pacientes com diagnóstico de desordens de humor, como demonstrado pelos achados de IMC, CC e triglicerídeos periféricos reduzidos neste grupo. Outros parâmetros pesquisados como possíveis biomarcadores para o comportamento suicida, a saber, colesterol total e frações, PCR, BDNF, leptina e S100B, não apresentaram diferenças em seus níveis entre pacientes com e sem TS. Apesar de estudos evidenciando uma correlação entre estas proteínas e colesterol total/frações com desordem mental e comportamento suicida, nossos dados não confirmaram esta associação.

Ainda é cedo para afirmar que estamos próximos de uma mudança de paradigma, mas certamente é um desafio que poderá trazer melhor compreensão dos mecanismos neurobiológicos do comportamento suicida e quiçá interromper a passagem para futuras gerações de uma herança, geneticamente herdada ou não, mas certamente não desejada.

Em suma, nossos dados reforçam a ideia de que a menor adiposidade observada nos pacientes com TS, aqui caracterizada por valores de IMC, CC e triglicerídeos periféricos reduzidos em relação àqueles sem histórico de TS, pode estar sinalizando uma comunicação alterada entre tecido adiposo-encéfalo. Por outro lado, a excessiva ingestão alimentar poderia corresponder a uma forma de amenizar mecanismos subjacentes ao comportamento suicida.

Tais parâmetros, portanto, são promissores para futuras pesquisas e talvez como biomarcadores em psiquiatria na avaliação de comportamento suicida.

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