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We are like a **FENIX:**
we are reborn from the ashes

EDITORIAL

NOW WE ARE FACULDADE EVANGÉLICA MACKENZIE DO PARANÁ (FEMPAR)

In 1943, during the World War II Curitiba was a small city, which did not have great options for specialized health treatment. At this time, Dr. Parisio Cidade, a doctor and pastor of the Presbyterian Church, felt himself challenged to create a hospital to care for needy people in Paraná and Santa Catarina. This idea affected the Presbyterian community of the city who carried out construction of the Evangelico Hospital of Curitiba.

On September 5, 1959 started our history with the hospital inauguration. A great event for the whole city ! The mission of the Hospital which was to treat the less fortunate was starting. Since its inauguration, the Evangelical Hospital already had the vocation for teaching in the health area and in the early 60's already had a body of medical students residing in the hospital.

In 1969, Professor Doctor Daniel Egg inaugurated the Faculdade Evangélica de Medicina do Paraná. His objective was to train highly qualified doctors. Right after the beginning of the classes of medical course, was verified the need for expansion of the hospital and then in 1970 was laid the cornerstone of the new building going from 150 to 550 the number of beds.

Already in the 70's, it started the Latu Sensu Post Graduation which, nowadays, graduates on average 80 specialists in medical degree per year in the most different areas.

Because of its educational expertise, in 1994, Strictu Sensu Post Graduation was created – master and doctorate levels - where more than 260 masters and doctors have already been trained in this Institution.

With 60 years of relevant services provided to the community of Paraná, today HUEM, is one of the largest private hospital complexes in Brazil, attends more than 1.5 million patients annually.

The medical students at the Evangelica Mackenzie Faculty of Paraná receives a generalist, holistic, humanistic, critical and reflexive education, that make possible their performance, guided by ethical principles, in the health-disease process in different levels of attention, in perspective of integrality with social responsibility and commitment to citizenship, as a promoter of the integral health of the human being.

The Medical Course completes 50 years of existence in this year. Today FEMPAR has contributed in a significant way, graduating medical professionals with high qualification and its teaching staff is formed in majority by Masters Degree and PHD ‘s graduated in this Institution.

Today we reverence the past with eyes in the future, highlighting the roots of this dream of faith, work and passion that motivated the development of our Institution. Teachers, technicians, researchers, collaborators of all kinds and all graduations. Human beings who welcomed and welcome the ideal of educating as profession of faith, as the target of life, as the task of existence.

If we are here today is because we are proud of our past. Our glances turn to the future where we are sure that there will always be in this institution professors, physicians who do not give up a good fight and who will be always inspired by Life, Joy and Virtue.

What we expect from the future: responsibility to be more and more great in health area and thus not only to train good professionals but professionals committed with their patients in quality and institutional values.

Professor Dr Carmen Paredes Marcondes Ribas

Director of Faculdade Evangélica Mackenzie do Paraná - Brazil

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Photo: Collection of Professor João Carlos Simões

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REVIEW
OFF-LABEL DRUGS USE IN TREATMENT OF DIABETIC NEUROPATHY
USO DE MEDICAMENTOS OFF-LABEL NO TRATAMENTO DA NEUROPATIA DIABÉTICA

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Key words: Diabetic neuropathy, Off-label use, Diabetes *mellitus*.
Descritores: Neuropatia diabética, Uso "off-label", Diabetes *mellitus*.

Abstract

Introduction: Diabetes mellitus is an important public health problem worldwide, and associated diabetic neuropathy is its most costly and disabling complication. With rising prevalence of painful diabetic neuropathy, it is important that we understand the best ways to treat this condition. Currently, physicians may prescribe several drugs "*off-label*" for diabetic neuropathy. The prescribing a drug without the indications for which the drug was originally approved by regulators is internationally known as prescribing *off-label*. **Endocrinol diabetes clin exp 2019 2000 - 2000.**
Objective: The aim of this study is to assess the evidences for *off-label* use of medication in diabetic neuropathy. **Methods:** Review study, describing the *off-label* medications used in diabetic neuropathy reported in the scientific literature. **Results**: In this integrative review of the published literature, *off-label* treatment of was generally associated with good short-term and long term outcomes. **Conclusion:** We concluded that conclude that the practice of *off-label* use in diabetic neuropathy has benefits, and in some situations is the only treatment available. **Endocrinol diabetes clin exp 2019 / 2064 - 2068.**

Resumo
Introdução: Diabetes mellitus é um importante problema de saúde pública mundial e a neuropatia diabética associada é uma complicação incapacitante e de elevado custo. Com o aumento da prevalência da neuropatia diabética dolorosa, é importante que entendamos as melhores maneiras de tratar essa condição. Atualmente, podem ser prescritos vários medicamentos "*off-label*" para neuropatia diabética. A prescrição de um medicamento sem indicações para o qual a droga foi originalmente aprovado pelos órgãos reguladores é conhecida internacionalmente como a prescrição *off-label*. **Objetivo:** O objetivo deste estudo é avaliar as evidências para o uso *off-label* de medicamentos em neuropatia diabética. **Método:** Estudo revisional, descrevendo os medicamentos *off-label* utilizados na neuropatia diabética relatados na literatura científica. **Resultados:** Nesta revisão integrativa da literatura, os tratamentos *off-label* da neuropatia diabética foram geralmente associados a bons resultados a curto e longo prazo. **Conclusão:** Concluímos que a prática do uso medicações *off-label* na neuropatia diabética tem benefícios, e em algumas situações é o único tratamento disponível. **Endocrinol diabetes clin exp 2019 / 2064 - 2068.**

INTRODUCTION

Manifold drugs are prescribed outside the terms of the marketing authorization ("*off-label*") from that approved by the health agency. *Off-label* uses of drugs are frequent in medical practice, even when without scientific evidence. *Off-label* therapy is defined as the use of medications for indications that is not mentioned in the approved labeling of the drug; using a drug outside of the recommended dosage range or duration of use; using a drug in certain unapproved patient populations, such as those defined by age, sex, or particular clinical parameters, or intentionally using a medication in a patient who has a known contraindication. It is legal, but there are implications for prescribers, outlined by regulatory bodies of health.

The *off-label* drug use is not without its danger. Thus, the Food & Drug Administration (FDA) has taken appropriate measures to regulate it. On September 25, 2015, the FDA proposed an amendment, to restrict the disclosure that is often used in *off-label* drug promotion (1). Brazilian legislation on *off-label* drug use still lacking further investigations and measures additionally (2).

Several studies have shown that this is a common practice in various healthcare settings, and studies in the United States of America (USA) have shown that *off-label* use may account for approximately 20% of prescriptions, or 150 million prescriptions per year (3,4).

Three broad categories of appropriate *off-label* use are identified: off-label use justified by high-quality evidence; use within the context of a formal research proposal; and exceptional use, justified by individual clinical circumstances (5). In USA, health surveillance institutions have no jurisdiction on medical practices and cannot restrict *off-label* prescriptions beyond educational campaigns.

The *off-label* medications use occurs in every specialty of medicine, but it may be more common in areas of medicine in which the patient population is less likely to be included in clinical trials (for example, pediatric, pregnant, or psychiatric patients) (6).

In this review, we will describe the *off-label* drugs used in diabetic neuropathy report in scientific literature.

OFF-LABEL USE

In the USA if a drug is approved for a purpose, is not illegal its *off-label* prescription. The prerequisites for ethical use of *off-labe*l drugs are: use in the context of formal research, exceptional and justified use by individual clinical circumstances, existences of comparative studies showing efficacy and safety, and informed consent.

In the specific case of diabetic neuropathy, the basic is its prevention with adequate metabolic control. Thus, the *off-label*

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prescribing in diabetic neuropathy has been substantiated by the opinion of experts, within prescribed standards and norms that are considered reasonable and modern, based on relevant literature and current prescribing practices. Therefore, physicians guided by evidence for clinical decision making prescribe less *off-label* drugs.

DIABETIC NEUROPATHY

Diabetic neuropathy is defined as "the presence of symptoms and/or signs of periphery nerve dysfunction in people with diabetes after the exclusion of other causes". The San Antonio Consensus Statement on Diabetic Neuropathy defined the condition as being a "demonstrable disorder, either clinically evident or subclinical in the setting of diabetes without other causes of peripheral neuropathy" (7), resulting from chronically high blood glucose. It can be one of the most frustrating and debilitating complications of diabetes because of the pain, discomfort and disability it can cause, and available treatments are not uniformly successful.

The pathogenic mechanisms of diabetic neuropathy mechanisms include excessive flux of polyols, associated with depletions in nerve and Schwann cell of myoinositol and rises in protein kinase C subunits, microangiopathy and hypoxia involving the peripheral nerve trunk, ganglia or spinal cord, oxidative and nitrative stress from free radicals, deficiency of growth factors, or their uptake and abnormal glycosylation of structural neuron proteins (8). Moreover, in a subpopulation of individuals with neuropathy, immune mechanisms may also be involved (9).

The diagnosis of diabetic neuropathy is not always easy, being based on your symptoms, medical history, and neurologic examination. The diagnostic algorithm is aimed at distinguishing the signs and symptoms of autonomic neuropathy with the use of quantitative autonomic function tests or those of small fiber neuropathy through quantitative sensory testing (10).

The objectives of painful diabetic neuropathy pharmacotherapy should be reduction of pain for maximum relief commensurate with acceptable side effects and restoration/ improvement in functional measures and quality of life. The choice of treatment is guided by the clinical status of the individual patient. The empirical approach to treatment and the common use of *off-label* treatments attest to the clinical need for a wide range of drug choices.

There are currently only three FDA-approved treatments for painful diabetic neuropathy: the anticonvulsant pregabalin, the serotonin–norepinephrine reuptake inhibitor (SNRI) duloxetine, and the opioid/SNRI tapentadol (11).

Most drug interventions to delay the progression of diabetic neuropathy are off-label prescriptions. We describes below the main drugs which support the off-label use for diabetic neuropathy.

OFF-LABEL TREATMENT OF DIABETIC NEUROPATHY

1. Anesthetic drugs

Studies show that intravenous lidocaine off-label ameliorates pain in diabetics with intractable neuropathic pain have failed to respond to or are intolerant of conventional available therapy (12).

Lidocaine blocks sodium channels and counteracts the hyperexcitability of peripheral nociceptors that contributes to neuropathic pain. In diabetic neuropathy are often used in combination with systemic analgesic medications, and lidocaine patches are a peripheral analgesic with minimal systemic absorption. A moderate to large effect on pain was seen in studies on the effectiveness of the lidocaine patch in painful diabetic neuropathy (13).

N-methyl-D-aspartate receptors have been an attractive target for treatment of chronic neuropathic pain for two decades. Ketamine, noncompetitive antagonist of Nmethyl-D-aspartate receptors, has been used in the off-label treatment of chronic neuropathic pain for almost 15 years. However, clinical studies suggest that the therapeutic effects of this class of drugs are mostly limited to patients with complex regional pain syndrome and painful diabetic neuropathy. The *off-label* ketamine has been used in diabetic neuropathy however randomized study, placebo-controlled trial examining topical 2% amitriptyline, 1% ketamine, and a combination in the treatment of neuropathic pain revealed no difference between groups. Optimization of doses may be required, at higher concentrations of these agents combined for produce significant analgesia (14).

Therefore, anesthetic drugs are currently *off-label* prescribed in the diabetic neuropathy with acknowledged benefits resulting from the fact that can neuropathic pain reduces with safety and efficacy.

2. Antiepileptic

Some antiepileptic drugs are used *off-label* for other conditions. In endocrinology, the antiepileptic drugs are frequently used to treat of diabetic neuropathy and more recently eating disorders or obesity.

The diabetic peripheral neuropathic pain has been treated with certain anticonvulsant agents. Among anticonvulsant agents, gabapentin it is considered to have a safety profile excellent, is relatively well tolerated, have few medication interactions and efficacious in the treatment of painful diabetic neuropathy. The exact mechanism of action of gabapentin is unknown, and the pain-modulating properties of gabapentin may be linked alteration of the synthesis and release of gamma-aminobutyric acid, binding to voltage-gated calcium channels, inhibition of voltage-gated sodium channels, and alteration of monoamine neurotransmitter release and blood serotonin levels.

Other anticonvulsant agent, carbamazepin began to be *off-label* used for trigeminal neuralgia after the publication in Lancet in 1962, before the discovery of much of what we now know about the neurophysiology of nociception and the neuropathology of neuropathic pain. Carbamazepine prevents repetitive firing of action potentials in depolarized neurons by blocking frequency, use, and voltage-dependent sodium channels, is metabolized in the liver, and the active epoxide metabolite is hydrolyzed to an inactive diol metabolite that is renally eliminated (15). Although diabetic neuropathy is a common problem in primary care practice, there are few data evaluating the effectiveness of carbamazepine for diabetic neuropathic pain. However, the *off-label* use of carbamazepine in diabetic neuropathy is effective for chronic pain (16).

The oxcarbazepine, one of the new derivatives of anti-epileptic agents, was found to possess antineuralgic properties in animal models of neuropathic pain. In humans, oxcarbazepine is metabolized via reduction and conjugation. Monohydroxy derivative of oxcarbazepine is the major pharmacologically active component after oxcarbazepine ingestion. Although its pharmaco-dynamical effects are similar to carbamazepine, the profile of oxcarbazepine has lack of side effects common to carbamazepine. Several double-blind, placebo-controlled trials have evaluated oxcarbazepine in painful diabetic neuropathy, and its efficacy in treating *off-label* painful diabetic neuropathy it seems to be useful at doses of 1800 mg/day, and the long term treatment is generally well tolerated in patients with painful diabetic neuropathy (17).

Lamotrigine is an anticonvulsant drug that act at the presynaptic membrane on voltage-dependent sodium channels, inhibiting the release of glutamate and aspartate evoked by the sodium-channel activator veratrine and was less effective in the inhibition of acetylcholine or gamma-amino butyric acid (GABA) release. The lamotrigine is used in the treatment of epilepsy and bipolar disorder. It is also used *off-label* as an adjunct in treating neuropathic pain, and has proven effective and safe in relieving the pain associated with diabetic neuropathy. However,

study showed that the lamotigine has not been effective for diabetic neuropathy, and due to side-effects and slow titration period is not generally recommended as a first-line treatment for neuropathic pain (18).

Topiramate is an antiepileptic drug whose mode of action is multifactorial and involves blockade of voltage-dependent sodium channels, potentiation of GABAergic transmission and inhibition of excitatory pathways through an action at α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor sites, and those multiple mechanisms of action may contribute to its anticonvulsive, anti-nociceptive, and putative neuro-protective properties. Recently, topiramate has been used *off-label* in other conditions such as bulimia nervosa, obesity, and neuropathic pain. The beneficial effects may also be related to the increasing and decreasing effects of the GABA and glutamate systems in the central nervous system. Topiramate has been used successfully in relieving the pain of painful diabetic peripheral neuropathy. Small pilot study with topiramate appeared to induce the growth of new nerve fibers and relieve symptoms of peripheral neuropathy. However, studies did not find topiramate to be significantly more effective than placebo in reducing pain scores in patients with painful diabetic polyneuropathy. Therefore, randomized controlled trials that specifically focus on the use of topiramate in patients with painful diabetic peripheral neuropathy is needed evaluation *off-label* use neuropathic pain syndromes, including diabetic peripheral neuropathy (19).

Valproic acid is antiepileptic drug used to treat chronic neuropathic pain, although is not licensed for this use. Valproic acid, acts on a variety of targets, including sodium channel blockade, increased GABA function, and modulation of N--methyldaspartate receptors, is primarily metabolized in the liver by b-oxidation and glucuronidation, its metabolites are excreted renally. Study with valproic acid showed significant role in the subjective improvement of diabetic neuropathy, with a unique advantage of low toxicity and favorable side effect profile, moreover provide significant improvement in pain scores as well as in electrophysiological parameters. However, in recent review the authors conclude that there is insufficient evidence to support the use of valproic acid as a first-line treatment for neuropathic pain (20).

Zonisamide mechanisms of action suggest that it would be effective in controlling neuropathic pain symptoms, and can be a useful therapeutic agent, presumably for both prevention and reversal of pathophysiologic pain. Multiple modes of action have been reported for zonisamide, including inhibition of sodium channels and T-type calcium channels, scavenging of free radicals, and blockade of nitric oxide synthesis. The relationships between these actions of zonisamide and its analgesic effects remain mostly unclarified. However, studies show that that the use of zonisamide is considered equivocal, and larger randomized, controlled trial are needed to establish the efficacy and tolerability for painful diabetic neuropathy (21).

Thus, despite of absence of current scientific clinical trials for use of antiepileptic drugs in diabetic neuropathy, based on pharmacological effects described above the medical practitioners are free to prescribe antiepileptic drugs for *off-label* uses in diabetic neuropathy.

3.Antidepressant

The first generation anti-depressants present tricyclic structure, thus they are in general described as tricyclic antidepressants. The second generation antidepressants are structurally very heterogeneous and the common ground is their pharmacodynamics effect-selective serotonin reuptake inhibition. While third generation anti-depressants are also structurally and pharmacodynamically heterogeneous, and are selective reuptake inhibitors of norepinephrine (22).

The most efficacious antidepressants for *off-label* use of neuropathic pain appear to be the amitriptyline, doxepin, imipramine, venlafaxine, and bupropion. These appear to be closely followed in efficacy by the desipramine, nortriptyline. Modestly effective antidepressants may include the paroxetine and citalopram. Ineffective antidepressants include fluoxetine.

There are several tricyclic antidepressants available for the *off-label* use of chronic pain. Clinical trials have shown than tricyclic antidepressant drugs are effective for patients with painful diabetic neuropathy. The dose of tricyclic antidepressants used to treat diabetic neuropathy is typically much lower than that used to treat depression.

Physicians have been using tricyclic antidepressants to treat neuropathic pain for years, without approved labeling from the Food and Drug Administration (FDA), and they are recommended as first-line therapy for diabetic peripheral neuropathic pain in appropriate patients. It their mechanism of action occur by their unique ability to inhibit presynaptic reuptake of the biogenic amines serotonin and noradrenaline, but other mechanisms such as N-methyl-D-aspartate receptor and ion channel blockade probably also play a role in their pain-relieving effect (23).

Of the tricyclic antidepressants the amitriptyline showed to be an effective treatment for painful diabetic neuropathy, where studies demonstrated a large reduction in pain. The imipramine and nortriptyline, have been studied in diabetic painful neuropathy and the results have been inconclusive, however nortriptyline is often used instead of amitriptyline because of reduced side effects (24).

The venlafaxine is a representative of newer generation of antidepressant drugs with increasing importance in the treatment of pain, that beyond reuptake inhibition of serotonin and norepinephrine, blocking of a1-adrenergic, histaminic, muscarinic and nicotinic receptors and blocking of ion conduction in calcium, sodium and potassium channels, weak dopamine reuptake inhibitor activity, and has mild N-methyl d-aspartate antagonism activity (25). Therefore, venlafaxine could be an alternative to classical tricyclic antidepressants for use in neuropathic pain, whether or not mood disorders are present.

The bupropion is chemical name of β-keto-3-chloro-N-tert-butylamphetamine, a substituted cathinone (β-ketoamphetamine) that binds selectively to the dopamine transporter, but it behavioural effects have often been attributed to its inhibition of norepinephrine reuptake, and also acts as a nicotinic acetylcholine receptor antagonist. Bupropion belongs to the chemical class of aminoketones and is similar in structure to stimulants cathinone and diethylpropion, and to phenethylamines in general. Bupropion is an antidepressant originally approved by the FDA in 1989 for the treatment of depression, and has been used in a variety of conditions, in addition to its FDA indications. In endocrinology bupropion has been used *off-label* in loss of weight, improvement in sexual functioning DM2, and diabetic neuropathy. Current evidence from clinical trials supports the use bupropion as medications in the treat of diabetic neuropathy it acts as specific inhibitor of neuronal noradrenaline reuptake and a weak inhibitor of dopamine reuptake (26).

The paroxetine is chemical name of (3S,4R)-3-[(2H-1,3--benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine, and is a selective serotonin reuptake inhibitor effective in the treatment of depression, and has also shown potential in the symptomatic *off-label* use of diabetic neuropathy. Study showed that 40 mg paroxetine/day significantly reduced the symptoms in peripheral diabetic neuropathy and was devoid of the often disturbing autonomic side effects (27).

The citalopram is chemical name of 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, is an antidepressant drug of the selective serotonin reuptake inhibitor class. It has U.S. FDA approval to treat major depression, and is prescribed *off-label* for other conditions, including diabetic neuropathy to reduce the symptoms. In a systematic review with meta-analysis of 25 randomised controlled trials the authors assessed the efficacy and safety

of antidepressants selective serotonin reuptake inhibitors – citalopram, in comparison with placebo in 2984 patients with painful diabetic neuropathy. Pain was reduced more than 50% or there was moderate relief of pain in patients receiving citalopram (OR 3.5) (28).

So the results of the studies support that the *off-label* treatment with antidepressant drug in patients with neuropathy diabetic, may prevent or delay the progression of neuropathic pain.

4.Antihypertensives

Clonidine is a α2-adrenergic receptor agonist that was originally approved as an oral product to treat hypertension. Prior reports from studies in humans have suggested that *off--label* prescriptions of clonidine may be effective in relieving neuropathic pain when applied topically to the painful area, and indicates that your efficacy depends on the relative level of functionality of nociceptors in the skin. However, based on a meta-analysis of the studies published the therapeutic efficacy of systematically administered clonidine was evaluated in chronic pain states, and showed that treatment with systemic clonidine is of no significant value (29).

Our study found only one study demonstrated that the antihypertensive clonidine was effective in neuropathy diabetic when applied topically.

5.Opioids

The role of opioids in diabetic neuropathy is nowadays more accepted. Higher opioid doses are often needed for neuropathic pain than for nociceptive pain, and most of the data are of *off-label* use. Sustained release preparations, including transdermal formulations, increase patient compliance. Of the 2 opioids that are available in transdermal formulation-fentanyl and buprenorphine-fentanyl is the most investigated, but based on the published data both seem to be effective, with low toxicity and good tolerability profiles, especially at low doses (30).

Morphine sulfate can relieve pain by multiple mechanisms, including a presynaptic effect on small afferent C fiber nerve terminals and a postsynaptic hyperpolarizing effect on spinal neurons. Study examined the effects of morphine in diabetic neuropathy showed that morphine had a small effect on pain and improved mood (31). However, patients taking opioids chronically may become tolerant and require higher than usual doses to maintain pain relief. Use with caution in patients with a history of substance abuse because of the potential for drug dependency.

Tramadol is a centrally acting analgesic for use in treating moderate to moderately severe pain. Studies showed that tramadol was effective and safe in treating the pain of diabetic neuropathy. Tramadol is a unique compound with both a weak opioid effect when compared to classical opioids, and a weak monoaminergic effect, when compared to tricyclic antidepressants, and its action would not be limited to neuropathic pain but also to suppress nociceptive pain (32). The studies showed that *off-label* use of tramadol is an effective treatment for neuropathic pain. Its efficacy is similar to that reported for antidepressants and anticonvulsants, but adequate direct comparisons are not available. Its use may be limited by side effects, but these are reversible and not life threatening.

Thus, opioids can be *off-label* prescribed in patients with neuropathy diabetic, with persistent neuropathic pain, because reduces the pain independent from glycemic control.

CONCLUSIONS

This study presented a descriptive review on *off-label* drugs use in treatment of diabetic neuropathy. When a doctor prescribes a drug for a use, or in a manner, not authorized by the FDA is called *off-label* prescribing. The current system allows drugs that are safe and effective for one indication could be used for any other indications without adequate safeguards. Thus, *off-label* drug use is just one aspect of the larger question about how to balance benefits, harms, and costs of medical interventions when technological advances are rapid, evidence is imperfect, and resources are finite.

Therefore, the use of *off-label* drugs in diabetic neuropathy is an alternative in the treatment of complications of diabetes, and its use has been demonstrated an improvement in signs and symptoms while specific medications yet not have been released for use on-label.

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ORIGINAL ARTICLE
ASSOCIATION BETWEEN OBSTRUCTIVE SLEEP APNEA-HYPOPNEA SYNDROME, INSULIN RESISTANCE AND NON-ALCOHOLIC FATTY PANCREATIC DISEASE

ASSOCIAÇÃO ENTRE SÍNDROME DE APNÉIA E HIPOPNÉIA OBSTRUTIVA DO SONO, RESISTÊNCIA INSULÍNICA E DOENÇA PANCREÁTICA GORDUROSA NÃO ALCOÓLICA

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Keywords: Obstructive sleep apnea; Insulin resistance; Non-alcoholic fatty pancreatic disease.
Descritores: Apneia obstrutiva do sono; Resistência à insulina; Doença pancreática gordurosa não alcoólica.

Abstract

Introduction: There is evidence of association between obstructive sleep apnea and insulin resistance (IR), as well as, to fatty deposition in the pancreas in a similar way to non-alcoholic fatty liver disease. **Objective:** Demonstrate the interaction between obstructive sleep apnea hypopnea syndrome (OSAHS), IR and non-alcoholic fatty pancreatic disease (NAFPD) by signaling pathway diagram. **Method:** To investigate the involvement of metabolic signaling pathway, a search was performed using the Kyoto Encyclopedia of Genes and Genomes (KEGG), and the signaling pathway mapping was performed using the automatic annotation server of the KEGG. The Modeller 9.19 package was used to predict 3D structure based on the homology modeling protocol. The signaling pathway map was realized using PathVisio program, a free available signaling pathway drawing software. Based on the 3-dimensional (3D) structure, we have designed several peptide activators of signaling pathway of NAFPD. **Results:** The contigs were taken from the KEGG database and their mapped transcription represents the signaling pathway of the main biomolecules that triggers NAFPD. The interaction between OSAHS, IR and inflammatory factors contributes to the possible development of fatty infiltration of pancreas, leading to loss of pancreatic β-cells function, and even have links to the development of other metabolic disease. **Conclusion:** The interaction between OSAHS and IR demonstrated through the signaling pathway, contributes to the possible development of NAFPD. **Endocrinol diabetes clin exp 2019 / 2069 - 2071.**

Resumo

Introdução: Há evidências de associação entre apneia obstrutiva do sono e resistência à insulina (IR), bem como a deposição gordurosa no pâncreas de maneira semelhante à doença hepática gordurosa não alcoólica. **Objetivo:** Demonstrar a interação entre a síndrome de apneia hipopneia obstrutiva do sono (SAHOS), a IR e a doença pancreática gordurosa não alcoólica (NAFPD) através do desenho de uma via de sinalização. **Método:** Para avaliar o envolvimento da via de sinalização metabólica, realizou-se uma pesquisa usando a Enciclopédia de Genes e Genomas de Kyoto (KEGG), e o mapeamento da via de sinalização foi realizado usando o servidor de anotação automático do KEGG. O software Modeller 9.19 foi usado para prever estruturas tridimensionais (3D), com base no protocolo de modelagem por homologia. O desenho da via de sinalização foi realizado usando o programa PathVisio, um software de domínio público para desenho de via de sinalização. Com base nas estruturas 3D, desenhamos os vários ativadores peptídicos da via de sinalização esteatose pancreática. **Resultados:** Os contigs foram retirados do banco de dados KEGG e sua transcrição mapeada representa a via de sinalização das principais biomoléculas que desencadeiam NAFPD. A interação entre SAHOS, IR e fatores inflamatórios contribui para o possível desenvolvimento de infiltração gordurosa do pâncreas, levando a perda de função das células-β pancreáticas e até mesmo o desenvolvimento de outras doenças metabólicas. **Conclusão:** A interação entre SAHOS e IR demonstrada através da via de sinalização, contribui para o possível desenvolvimento de NAFPD. **Endocrinol diabetes clin exp 2019 / 2069 - 2071.**

INTRODUCTION

The non-alcoholic fatty pancreatic disease (NAFPD) is defined as an injury that varies from the excessive fatty infiltration of the pancreas without fatty replacement to pancreatic inflammation, pancreatitis which may progress to pancreatic fibrosis (1). The NAFPD may occur in function of replacement by adipocytes of dead pancreatic acinar cells or accumulation of fat associated with metabolic disease. Several words of similar meaning for increase of fatty in pancreas have been used in the literature; however, the NAFPD term should be intended to accumulation of fatty in pancreas associated with obesity and metabolic syndrome (2). Few studies have been evaluated the prevalence of NAFPD which was estimate between 16% and 35% in adult population and 10% in a pediatric population (3,4).

The obstructive sleep apnea hypopnea syndrome (OSAHS) it's due to usual event of absence or reduction in breathing in the course of sleep regardless of a regular effort to breathe normally. Is characterized by an apnea-hypopnea index (AHI) of 15 or greater or an AHI of 5 or greater with frequent arousals during sleep, in addition to disruptive snoring and excessive daytime sleepiness, and has been associated to several adverse health outcomes, including insulin resistance (IR) (5). The prevalence of OSAHS is 3%–7% in men and 2%–5% in women (6).

The IR is a metabolic disorder defined clinically as low capability of insulin in increase glucose uptake and utilization in target tissues, which may be due to several mechanisms, among which include protein genetic changes of the insulin action cascade, fetal malnutrition, and increases in visceral adiposity (7).

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The OSAHS has been associated with the degree of IR which in turn would take pancreatic adipocyte infiltration, with consequent NAFPD (8,9).

We focus on OSAHS and the roles of inflammatory transcription factors inductors in IR and their involvement in pathogenesis of NAFPD, with the objective of demonstrate the association between OSAHS and NAFPD by signaling pathway diagram.

ASSOCIATION BETWEEN OSAHS AND NAFPD

The OSAHS seems to be one of the key factors in the development of the NAFPD, and this was suggested in a recent study (10).

There is data suggesting that OSAHS is a risk factor for dyslipidemia because it is independently associated with metabolic syndrome with increased levels of triglycerides and reduced levels of high-density lipoproteins (11). This association would be mediated by lipid clearance reduction, increased lipolysis, and regulation of lipid synthesis in the liver. Moreover, OSAHS can influence development of type 2 diabetes (DM2) in predisposed individuals in function of hypoxic damage to pancreatic β-cells, because the intermittent hypoxia taking to hormonal derangements inducing enhanced lipid synthesis and inflammation, contributing for pancreatic fatty infiltration (12).

A relation between metabolic alterations and fatty infiltration of the pancreas were showed in various studies with animals who considered the hypothesis of that the fatty infiltration of the endocrine pancreas would lead to a change in insulin secretion and the development of DM2 (13-15).

The prevalence of OSAHS is directly proportional to increases in body weight gain and, consequently, to an increase in body mass index (BMI) (16). Likewise, studies show that NAFPD is closely associated with BMI (17).

Therefore, factors such as increase in BMI, IR, damage to pancreatic β-cells leading to DM2, dyslipidemia, and metabolic syndrome common to OSA and NAFPD, could explain the interaction between both.

MATERIAL AND METHOD: MODEL

Signaling pathways regulate cellular decisions, and mathematical models have been used in elaboration of biological signaling pathways. To investigate the involvement of metabolic signaling pathway, a search was performed using the KEGG (Kyoto Encyclopedia of Genes and Genomes, www.kegg.jp), a databases containing biological information about signaling pathway maps, extracting networks biological processes, molecular interaction, as well as protein domains data. We investigated a total of 46 signaling pathways in the KEGG databases, and for each pathway we identify all the related protein with obesity, IR, DM2, dyslipidemia, and metabolic syndrome common to OSA and NAFPD, and we compared the proteins and interactions of ten pathways. The Modeller 9.19 package was used to predict 3D structure based on the homology modeling protocol. The signaling pathway map design was realized using PathVisio program, a free available signaling pathway drawing software. Based on the 3-dimensional (3D) structure, we have designed several peptide activators of signaling pathway of NAFPD.

RESULTS

Signaling pathway design

As shown in Figure 1 multiple mechanisms underlying NAFPD are shown, and your interaction between OSAHS.

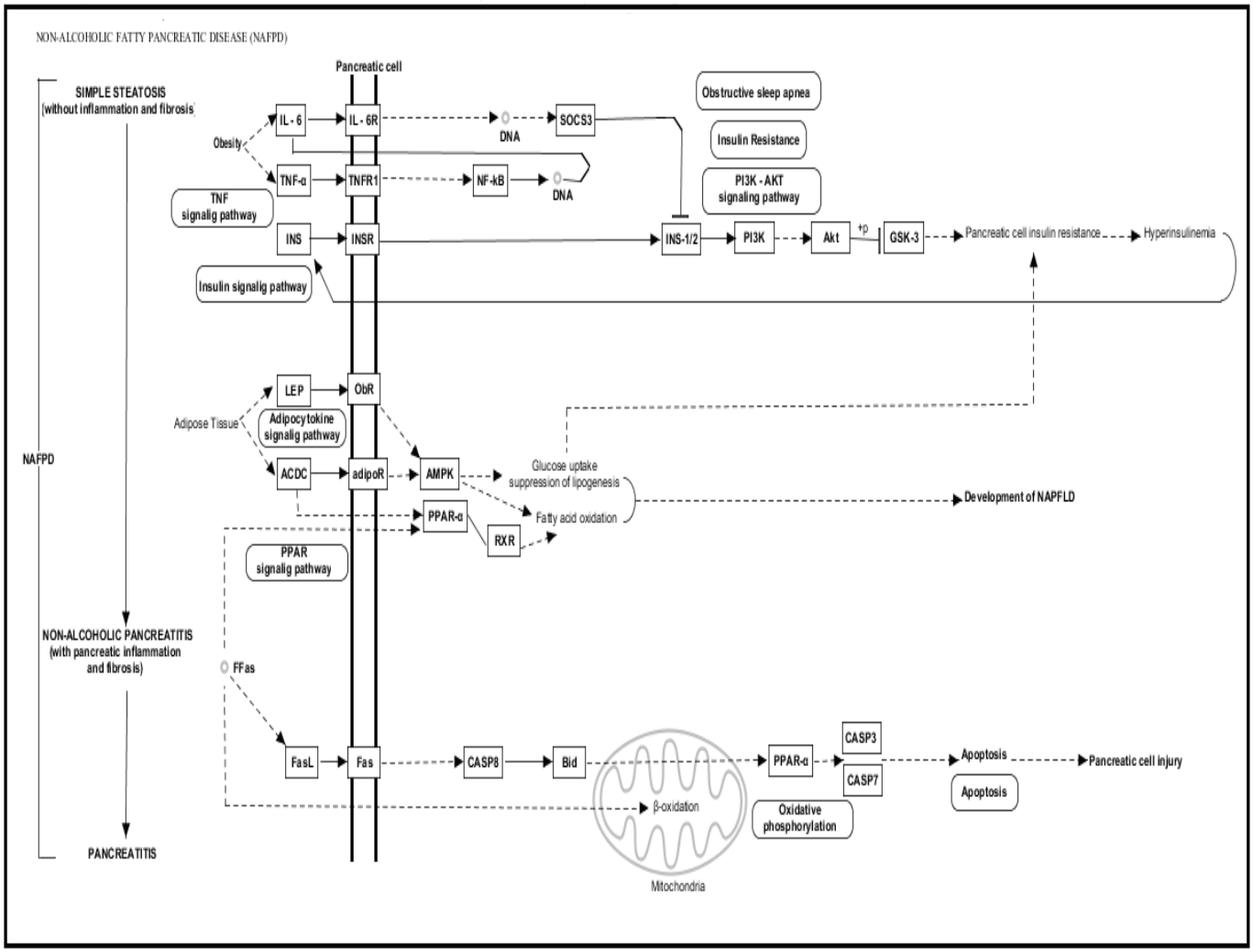

Figure 1. Signaling pathway of non-alcoholic fatty pancreatic disease model.

DISCUSSION

NAFPD signaling pathway

The NAFPD represents a spectrum ranging from simple steatosis to more severe steatopancreatitis with pancreatic inflammation and fibrosis, known as non-alcoholic steatopancreatitis (NASP). The NASP may further lead to pancreatic fibrosis. This diagram shows a stage-dependent progression of NAFPD. In the first phase of NAFPD, adiposy tissue accumulation has been demonstrated as activators of inflammatory factors. The main cause is the induction of IR, which leads to a defect in insulin suppression of free fatty acids (FFA) disposal (18). Moreover, transcription factor Peroxisome proliferator-activated receptor-α (PPAR-α), activate key enzymes of lipogenesis and increase the synthesis of FFA in pancreas (19). In the second phase, as a consequence of the progression to NASP, the production of reactive oxygen species is enhanced due to oxidation stress through mitochondrial β-oxidation of fatty acids and endoplasmic reticulum stress, leading to lipid peroxidation. The lipid peroxidation can further cause the production of cytokines, caspases, promoting cell death, inflammation and fibrosis (20).

OSAHS induces IR an inflammatory state directly associated to the increase in visceral fatty that is an abundant source of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and profibrogenic adipokine leptin. In addition, the development of IR, is also caused by the inactivation of the phosphoinositide-3-kinase (PIK3) regulatory → serine/threonine kinase (STK) signaling pathway leading to the progression of pancreatic cell IR and consequent NAFPD.

The development of IR involves numerous mechanisms underlying including increment of phosphorylation of IRS (insulin receptor substrate) protein by protein kinase C, c-Jun N-terminal protein kinase 1 and inhibitor of nuclear factor kappa B kinase subunit beta (21). It also involves increased IRS-1 proteasome damage by mammalian target of rapamycin (mTOR), besides reduction of activation of signaling molecules among them the PI3K and protein kinase B (AKT), and increase in acting of phosphatases encompassing protein tyrosine phosphatase (PTPs), phosphatase and tensin homolog (PTEN), and protein phosphatase 2A (PP2A) (22).

CONCLUSION

The OSAHS and NAFPD have a common pathway with obesity, IR, DM2, dyslipidemia, and metabolic syndrome The factors that lead to the progression of simple steatosis to NASP are likely to be multiple and complex involving transcription factors in inflammation-induced IR. In this way, we proposed a model of interaction OSAHS and NAFPD by signaling pathway map.

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ORIGINAL ARTICLE
EXPERIMENTAL RESEARCH ASSOCIATIONS BETWEEN FOOD INTAKE, BODY MASS, AND GLYCEMIA LEVELS IN DIABETIC RATS TREATED WITH AN AQUEOUS EXTRACT OF BAUHINIA FORTIFICATA (FABACEAE)

ASSOCIAÇÃO ENTRE INGESTÃO ALIMENTAR, MASSA CORPORAL E PADRÕES GLICÊMICOS EM RATOS DIABÉTICOS TRATADOS COM EXTRATO AQUOSO DE BAUHINIA FORFICATA (FABACEAE).

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Keywords: Experimental diabetes mellitus; Phytotherapeutic drugs; Diet high-fat
Descritores: Experimental diabetes mellitus; Phytotherapeutic drugs; Diet high-fat

Abstract

Background: A tea made from Bauhina *forficata* is widely used as a complementary therapy to treat diabetes mellitus type 2, a pathology associated with a hypercaloric diet and obesity. **Objectives:** The present study sought to relate food intake, body mass, glycemia, and glucose metabolism in male rats of the Wistar hyperglycemic lineage treated with an aqueous extract (AqE) of B. *forficata*. **Methods:** Twenty four Wistar lineage male rats were divided into four experimental groups. Groups G2, G3 and G4A were fed with a hyperlipidic diet. After the induction of hyperglycemia in those animals, groups G3 and G4 were treated with an AqE of B. *forficata*. The data were analyzed using bivariate ANOVA, followed by the Bonferoni test. **Results:** The analyses evidenced that body mass increases were proportional to increases in food intake and glycemia. After treatment with the AqE of B. *forficata*, those parameters became reduced, indicating the efficiency of that phytotherapy as an alternative treatment. Group G2 demonstrated a reduction of glucose metabolism as a consequence of increased food intake. **Conclusion:** The present study evidenced that an *in natura* tea made from B. *forficata* reduced glycemia and body mass increases more effectively than commercial preparations, although no differences were observed in terms of food intake and glucose metabolism in either group after treatment. **Endocrinol diabetes clin exp 2019 / 2072 - 2075.**

Resumo

Introdução: O chá de B. *forficata* é mundialmente utilizado como terapia complementar do diabetes mellitus tipo 2, uma patologia muitas vezes secundária a dieta hipercalórica e obesidade. **Objetivo:** O presente estudo pretende relacionar ingestão alimentar, massa corporal, glicemia e metabolização da glicose em ratos machos da linhagem Wistar hiperglicêmicos tratados com extrato aquoso (AqE) de B. *forficata*. **Métodos:** Foram utilizados 24 (vinte e quatro) ratos machos da linhagem Wistar, divididos em 4 grupos experimentais. A dieta hiperlipídica foi fornecida aos grupos G2, G3 e G4. Após a indução da hiperglicemia nos animais, realizou-se o tratamento com o AqE de B. *forficata* para G3 e G4. Os dados foram submetidos a ANOVA bivariada seguida de teste de Bonferoni. **Resultados:** As análises evidenciam que o aumento da massa corporal foi proporcional ao aumento da ingestão alimentar e da glicemia. Ao passo que após o tratamento, esses parâmetros reduziram demonstrando a eficácia da fitoterapia como forma alternativa de tratamento. Ademais, observamos que G2 apresentou redução da metabolização da glicose com consequente aumento da ingestão alimentar. **Conclusão:** O presente estudo evidenciou que o chá da planta *in natura* foi capaz de reduzir a glicemia e a massa corporal mais efetivamente do que a amostra comercializada, entretanto, não observamos diferença na ingestão alimentar e na metabolização da glicose em ambos os grupos após a terapêutica realizada. **Endocrinol diabetes clin exp 2019 / 2072 - 2075.**

INTRODUCTION

Increases in obesity and excessive weight gains among children, adolescents, and adults in recent decades have become serious public health problems throughout the world (1). Demographic, socio-economic, and epidemiological changes in Brazil have resulted in changes in the nutritional patterns of theirs citizens, with progressive nutritional degradation and increases in obesity (2,3), Hyperlipidemia (4,5) and diabetes mellitus type 2 (DM2) (5) are frequently associated with obesity and intimately related to cardiovascular diseases (6,7).

Studies have attempted to elucidate and combat the principal factors contributing to the development of obesity and its association type 2 diabetes (8). Many of those studies have used animal models capable of demonstrating hyperlipemic conditions, or even DM2, with the goal of developing alternative therapeutics (9,10).

According to Oliveira et al (11-12) diets rich in carbohydrates, lipids, and proteins will result in weight gains and generate hyperglycemic symptoms in Wistar line male rats. That successful model of hyperlipemic induction made by Oliveira et al (11) demonstrated the efficiency of hyperglycemia induction by a hyperlipidic diet (HD) and successful treatment of both *in natura* and commercial preparations of Bauhinia *forficata* (10,11).

B. *forficata* leaves are widely used in popular medicine to combat DM2. Aqueous extracts of those leaves have demonstrated hypoglycemic activity and effective reductions in blood triglycerides, total cholesterol, and LDL levels (12, 13).

According to Engel et al (2008), the flavonoid kaempferol present in that plant stimulates beta-pancreatic cells to liberate insulin into the bloodstream (12). Earlier *in vitro* studies demonstrated that kaempferol diminished serum glucose levels by increasing uptake of glucose capture by adipose tissue through insulin stimulation of adipocytes (13). Kaempferol is known for its beneficial effects in treating diabetes symptoms

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and for preventing oxidative damage to β pancreatic cells (14).

There is ample evidence that the control of glycemia (15) and dyslipidemia (16) can result in significant reductions in microvascular and macrovascular complications in diabetic patients. Additionally, the efficiencies of alternative therapeutics have been definitively proven, such as the use of phytotherapeutics in complementary treatments of those pathologies (9,10,17)

The present study sought to associate food intake, body mass, glycemia levels, and glucose metabolism in Wistar lineage hyperglycemic male rats submitted to HD and subsequently treated with AqE of B. *forficata*.

MATERIAL AND METHODS

Animals

Twenty-four male rats (Wistar line), 60 days old, from the Biotherium at Iguaçu University (UNIG) were used. The animals were maintained during the experimental period at a constant temperature of 23 ± 1 ºC, under an artificial 12/12 photoperiod, with free access to food and water.

Ethical aspects

All of the procedures used here were performed according to the principles of animal experimentation and followed the norms established by the Brazilian Regulations of Animal Experimentation. Licensing (protocol: PEBIO/UNIG N.º 007/2017) was obtained from the Commission of Ethics for Animal Use (CEUA).

Diets

The normocaloric diet (ND) consisted of a commercial rat diet (Nuvilab®), containing by weight: 19.0% protein, 56.0% carbohydrate, 3.5% lipids, 4.5% cellulose, and 5% vitamins and minerals, totaling 17.03 kJ/g (10).

The hyperlipidic diet (HD) consisted of a mixture of hypercaloric foods in the following proportions: 15 g of the standard ration (Nuvilab®), 10 g of dried peanuts, 10 g of milk chocolate, and 5 g of "maisena" crackers. Those ingredients were ground, mixed, and offered in the form of pellets containing (by weight): 40% protein, 48.0% carbohydrates, 20.0% lipids, 4.0% cellulose, and 5.0% vitamins and minerals. The energetic content of the hyperlipidic diet was 21.40 kJ/g (18).

Aqueous extracts of B. *forficata* leaves

The aqueous extract of the standard (*in natura*) sample of B. *forficata* was prepared from an infusion of leaves (150 g leaves / liter of water). The commercial samples were prepared using the entire contents of their packages (50 g material / 500 ml of water) as recommended on the labels. The extracts were then filtered and concentrated under vacuum to obtain the Aqueous Extracts (AqE) used in the experiments. The extracts were divided into aliquots and maintained in a freezer until needed (10).

Experimental groups

The animals were distributed among four groups (n = 6 each). Group G1 (Control) was fed a normal diet ND diet during the entire experiment, and received no treatment with AqE B. *forficata*. Groups G2, G3, G4, were fed a HD diet between 60 and 120 days of life, followed by a DN diet until 150 days. Once hyperglycemia was established, groups G3 and G4 were forced-fed with an AqE of B. *forficata* between 120 and 150 days of life according to the following division: G3 with an *in natura* sample; G4 with a commercial sample. Group G2 (hyperglycemic control) received no additional treatment.

The blood glucose levels

Glycemia monitoring was performed after 12-hours of fasting; blood was collected from the caudal vein of the animals and deposited on disposable test strips that were read by a glucose meter (G- TECH) at 60, 90, 120 and 150 days of life (10).

The body mass

The animals were weighed on a weekly basis during the experiments using a digital balance (Filizolla; precision 0.5 g) (19).

The food intake

Food intake levels were monitored twice every week using the remains/ingested technique. The diet offered (500 g) was added to the feeders twice every week and, when renewed, the food remains were subtracted from the offered weights – representing the consumption of each animal (19).

Oral glucose tolerance test

Oral glucose tolerance tests (OGTT) were performed with animals during the last week of the experimental period, after 12-hours of fasting. The first blood collection was performed by making an incision in the extremity of the animal's tail (time 0). A solution of 50% glucose (to prepare a dose of 2 g/kg body weight) was administered to the animals by forced-feeding, and blood samples were collected after 30, 60, 90 and 120 minutes to determine glucose levels. A single incision at the tail extremity was sufficient to collect all of the blood samples required. Blood glucose concentrations were determined using a glucose meter (G-TECH) and a glycemia curve was plotted using GraphPad Prism 6.0 software for Windows (11).

Statistical analyses

Bivariate Variance Analysis (ANOVA), followed by the Bonferroni post-test was used to analyze and compare glycemia levels and glucose tolerance tests. The results were expressed as means and were considered significant when $p<0.05$. The analyses were performed and the graphs plotted using GraphPad Prism 6.0 software for Windows.

Results and Discussion

After inducing hyperglycemia and undertaking the different treatments with the AqE of B. *forficata* in groups G3 and G4, bivariate ANOVA followed by the Bonferoni test evidenced that there were significant differences between the variables (body mass, food intake, glucose metabolism, hyperglycemia) as accompanied after 120 days of life ($p < 0.05$) (Figure 1 a – d).

In terms of body mass (Figure 1 a), hyperglycemia was induced in animals exposed to a HD (11, 18). In the present study, the animals exposed to the HD diet (G2, G3 and G4) demonstrated significant increases in body mass up until 120 days of life. After that time, the G2 group (hyperglycemic control) demonstrated a discrete increase in body mass; the G3 group (*in natura* treatment with the AqE) demonstrated a decrease in body mass (no previous reports of the use of B. *forficata* tea reducing body mass were encountered in the literature); the G4 group (commercial sample) demonstrated significant increases in body mass even after ingesting the AqE.

It has been established that increasing body mass can provoke pre-obesity and obesity – a risk factor in the evolution of endocrine disturbances such as DM2, among other morbidities. Body mass also considerably influences the development of cardiovascular disease complications – the principal cause of death among DM2 patients (20, 21, 22).

In relation to food intake (Figure 1 b), we observed that the rat groups fed the HD showed statistically higher consumption rates than those offered DN between 90 and 120 days of life ($p < 0.05$). That feeding behavior was reflected in weight gains and increased blood glucose levels in groups G2, G3 and G4 (Figure 1 a – c). Long-term HD diets can increase the quantities of adipose tissue in animals as well as induce hyperphagia and increased fat consumption (23).

Treatment with AqE of B. *forficata* did not generally alter food consumption levels. We did not observe intake reductions between 120 – 150 days of life in G1 as compared to the other

groups during that period even though they were all supplied with the DN diet. The statistical analyses indicated that in spite of the change in their diet, the hyperglycemic control animals (G2) maintained high food intake rates (Figure 1 b). That result indicated that the metabolism of bloodstream glucose by the G2 group became significantly altered (OGTT test) (Figure 1 d), and glycemia levels were not reestablished at the end of the test (120 minutes) to initial levels (0 minutes) as was observed in the other groups, resulting in an increase in food intake due to the non-absorbance of glucose.

Still in relation to the OGTT (Figure 1 d), the groups exposed to AqE of B. *forficata* treatments demonstrated responses similar to those of G1 in terms of glucose metabolism. That result evidenced that the B. *forficata* treatment acted to effectively increase insulin liberation by beta pancreatic cells (the expected effect of Kaempferol) (12).

The hyperglycemia induced by the HD was reported in earlier studies (10, 11, 23). Considering all of the variables together, it could be seen that increases in glycemia levels were accompanied by increases in body mass and food intake (Figure 1 a – c). Chronic hyperglycemia is a preponderant risk factor for macrovascular complications and can eventually result in thrombosis and damage to the coronary arteries and involve into an acute coronary syndrome (25).

It is important to note the differences in the glycemia curves among the different groups fed with the HD diet between 90 and 120 days of life and the control group (Figure 1 c) – with reductions in blood glucose levels in the control group being seen in contrast to increases in the other groups. The administration of an AqE of B. *forficata* significantly reduced glycemia in the test animals, confirming the efficiency of that tea as an alternate therapeutic treatment, although the most significant reductions were evidenced among the animals treated with the *in natura* extract.

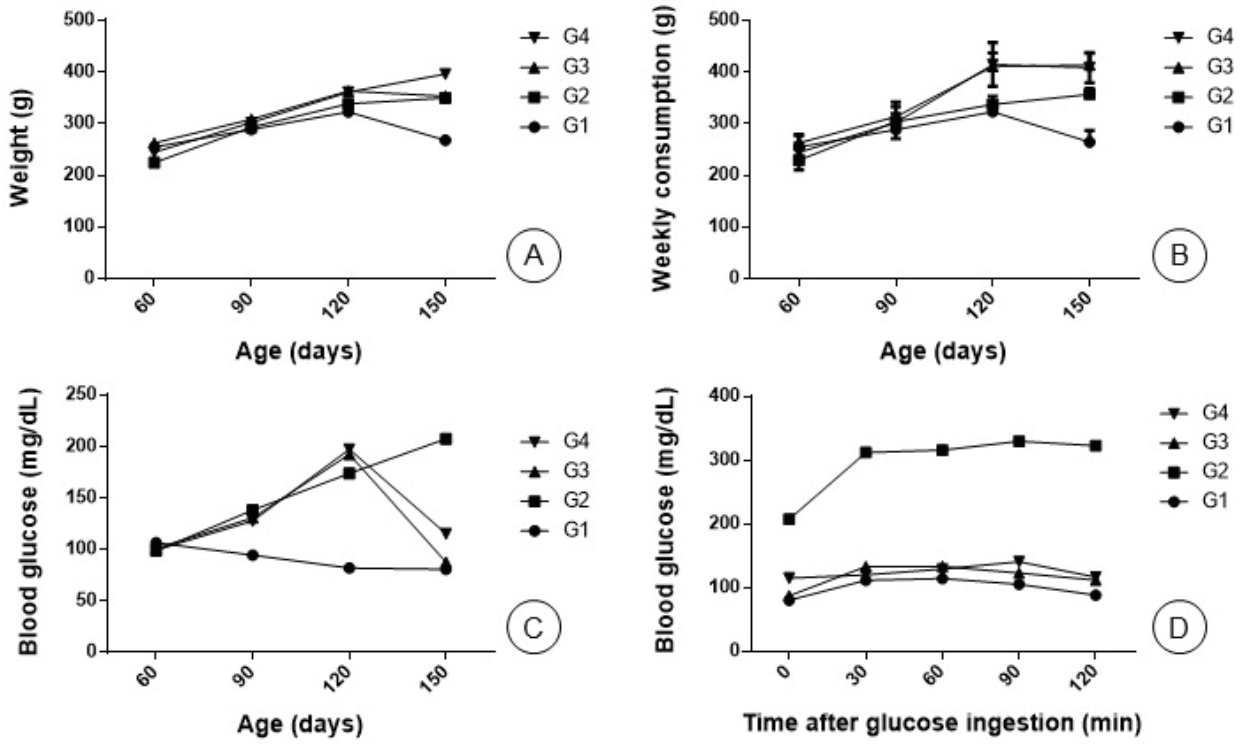

Figure 1. Statistical analyses with variables studied. (ANOVA bivariate post Bonferoni test, $p < 0.05$). A) Evolution of body mass in 60, 90, 120 e 150 days. Note that the groups feed HD have a substancial increase of weight until 120 days. B) Weekly consumption. Note that the groups feed with HD presents had high intake. C) Concentration of blood glucose in 60, 90, 120 and 150 days. Note the reduction of glucose levels between 120 and 150 days after treatment with G2 and G3. D) Concentration of blood glucose during oral glucose tolerance test. Note that G3 and G4 restore the glucose metabolization after treatment, however G2 indicates that glucose metabolization is damaged in hyperglycemic rats

Although phytotherapies are slowly becoming integrated into many traditional therapies, their indiscriminate or inadequate (low active contents in commercial samples) use can also result in severe collateral effects (24); additionally their contamination by pathogenic microorganisms can compromise their efficiency and/or safe consumption (10).

Conclusion

The present study evidenced that an *in natura* tea prepared from B. forficata reduced glycemia levels and body mass gains more effectively than commercial samples, although no differences between them were observed in terms of food intake and glucose metabolism. Recent studies have shown that commercial phytotherapeutics are potentially dangerous to public health, as they can become contaminated by pathogenic agents. As such, the safe and secure use of plant materials for medicinal purposes will require constant vigilance and care to avoid possible collateral effects due to their inadequate use or the consumption of samples with unacceptable contamination levels.

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ORIGINAL ARTICLE
TOPICS IN MEDICAL CLINIC
LUPUS HEADACHE: A CASE CONTROL STUDY IN BRAZILIAN PATIENTS

CEFALEIA NO LÚPUS: UM ESTUDO CASO-CONTROLE EM PACIENTES BRASILEIROS

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Key words: Systemic lupus erthematosus, Headache, Migraine, Quality of life
Descritores: Lúpus eritematoso sistêmico, Cefaléia, Enxaqueca, Qualidade de vida

Abstract

Background: Headache is considered a neuropsychiatric manifestation of systemic lupus erythematosus (SLE). Although its association with SLE and its characteristics are debated. Aim: To study the headache prevalence in SLE patients comparing it with healthy controls. **Methods:** We studied 53 SLE patients and 53 controls for the presence of headaches according to Guidelines of International Headache Society. Disease activity (by SLE Disease Activity Index or SLEDAI), clinical and serological profile and pain intensity measured by VAS (visual analogic scale from 0-10) were collected simultaneously. Those with migraine filled the MIDAS questionnaire or (Migraine Disability Assessment Questionnaire). **Results:** There was a high prevalence of headache in both groups (69.8% in SLE and 66% in controls, p=0.67) and migraine (47.1% in SLE and 41.5% in controls; p=0.55). VAS of pain and MIDAS did not show differences in those two groups (p=ns). It was not possible to associate the presence of headache in general or of migraine with any clinical finding or auto antibody, neither with SLEDAI. The MIDAS showed a weak correlation with SLEDAI (rho=0.37; 95%CI= 0.10-0.58; p=0.006). **Conclusions**: We could not prove that headaches were more common in lupus patients. We also could not associate the presence of headaches in general or migraine with a pattern of clinical or serological variables. In patients with migraine, a weak correlation of disease activity with quality of life was noted. **Endocrinol diabetes clin exp 2019 / 2076 - 2080.**

Resumo

Justificativa: A cefaleia é considerada uma manifestação neuropsiquiátrica do lupus eritematosos sistêmico (LES). Entretanto sua associação com LES e suas características são debatidas. **Objetivo:** Estudar a prevalência de cefaléia em pacientes com LES comparando-a com a de controles saudáveis. **Métodos:** Foram estudados 53 pacientes com LES e 53 controles para a presença de cefaléia de acordo com as Diretrizes da Sociedade Internacional de Cefaléia. A atividade da doença (pelo índice de atividade de doença de SLE ou SLEDAI), o perfil clínico e sorológico e a intensidade da dor mensuradas pela EVA (escala visual analógica de 0-10) foram coletadas simultaneamente. Aqueles com enxaqueca preencheram o questionário MIDAS (enxaqueca questionário de avaliação de incapacidade). **Resultados:** Houve alta prevalência de cefaléia em ambos os grupos (69,8% no Les e 66% nos controles, p = 0,67) e enxaqueca (47,1% no Les e 41,5% nos controles; p = 0,55). As EVAS de dor e resultados do MIDAS não mostraram diferenças nos dois grupos (p = ns). Não foi possível associar a presença de cefaléia em geral ou de enxaqueca com qualquer achado clínico ou auto anticorpo, nem com SLEDAI. O MIDAS apresentou fraca correlação com SLEDAI (Rho = 0,37; 95% IC = 0,10-0,58; p = 0,006). **Conclusões:** Não foi possivel provar que as cefaleias são mais comuns em pacientes com lúpus. Também não foi possível associar a presença de cefaléias em geral ou enxaqueca com um padrão de variáveis clínicas ou sorológicas. Nos pacientes com enxaqueca, uma fraca correlação da atividade da doença com qualidade de vida foi observada. **Endocrinol diabetes clin exp 2019 / 2076 - 2080.**

INTRODUCTION

Lupus headache is one of the clinical expressions of systemic lupus erythematosus (SLE) classified as a neuropsychiatric manifestation of this diseases by the American College of Rheumatology (ACR)/1999 (1). It is also a symptom to be considered when disease activity is being judge and it has a high score in the SLEDAI (SLE disease activity index) (2). Nevertheless, it is very difficult to be certain when a lupus patient has headaches because of this disease, as this is a very common symptom in general population. The prevalence of headache in lupus has been questioned. Some authors believed that SLE patients have more headaches than healthy population (3,4) while others denied it (5). Association with disease activity has also been debated (5,6), as well as the link of migraine with antiphospholipid antibodies and Raynaud's phenomena (6,7,8,9,10). To judge if the headache is caused by the SLE or not is important while choosing treatment. Some authors indicate glucocorticoid when the lupus etiology is considered (11).

In this context, we aimed to analyze the prevalence of headache in a cohort of SLE patients from Southern Brazil, comparing it with the prevalence of controls as well as its repercussions in quality of life. We also aimed to verify if migraine was associated with SLE clinical and serological variables and with disease activity.

MATERIAL AND METHODS

This is a cross-sectional study approved by the local Committee of Ethics in Research; all participants signed a consent. It include a convenience sample of SLE patients that come for regular consultation in a University Evangélico Mackenzie Hospital during a six months period and that agreed to participate in the study. To participate in the study, they must fulfilled at least four criteria of Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus

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(SLICC/ACR) classification criteria for SLE diagnosis (12) and to have more than 16 years of age at disease onset. Pregnant women, patients with other chronic diseases and uncontrolled hypothyroidism as well as those with headache secondary to organic causes were excluded. Patient's companions formed the control group. Patients and controls were interviewed for the presence of migraine in the past 6 months that was classified according to the Guidelines of International Headache Society (ICHD-3) (13).

Those with headache were invited to classify the degree of pain in a visual analogic scale (VAS) from zero to ten (zero=no pain; 10=worst scenario). To study the interference of this symptom in the quality of life, patients and controls filled the SF (Short Form Healthy Survey)-12 (14) and those classified as having migraine also filled the MIDAS (Migraine Disability Assessment Questionnaire) (15). SF-12 is quality of life measurement instrument that goes from 0-100 in which 100 is the best scenario and it is divided in mental and physical domains. MIDAS is an instrument to measure the repercussion of migraine in a patient's quality of life.

Epidemiological (age, gender, age at disease onset, auto declared ethnic background and tobacco use), clinical (malar rash, photosensitivity, oral ulcers, discoid lesions, serositis, glomerulonephritis, convulsions, psychosis, hemolytic anemia, leukopenia, lymphocytopenia and arthritis according to the definition of 1997 ACR classification criteria for SLE (16) and considered in a cumulative way) and serological data [anti ds DNA, anti Ro/SS-A; anti La/SS-B, anti-RNP, anti-Sm, aCl (anticardiolipin) IgG, aCl IgM, LA (or lupus anticoagulant), rheumatoid factor and direct Coombs] were extracted from the charts. At our institution anti Ro/SS-A, anti La/SS-B, anti RNP, anti Sm, aCl IgG, aCl IgM were done by ELISA (using ALKA and Orgentec Kits®), anti dsDNA is done by immunofluorescence technique (IFT) using Crithidia luciliae as a substrate. Lupus anticoagulant is searched through a screening test, the dRVVT (dilute Russell viper venom test), and mixing patient's plasma with normal plasma and confirmed by RVVT. Presence of antiphospholipid antibody syndrome was diagnosed according to Sidney criteria (17). Disease activity was evaluated through the SELENA-SLEDAI and computed without the headache variable (2).

We collected the data in frequency and contingency tables. Shapiro Wilks test was used to judge normality and central tendency was expressed in mean and standard deviation (SD) or median and interquartile rate (IQR) accordingly. Comparison of nominal data was done by Fisher and chi-squared test; of numerical data with unpaired t test and Mann Whitney test. Correlation were done using Spearman test. The significance adopted was of 5%.

RESULTS

We included 106 individuals: 53 SLE patients and 53 controls paired for age (p=0.97) and gender (p=0.76). The main characteristics of studied population is on Table 1.

Table 1- Main epidemiological, clinical, serological and treatment characteristics of studied population

Variable	N (%) or central tendency
Mean age (years)	38.25±11.62
Mean age at disease onset (years)	27.79±10.68
Female gender	47 (88.6)
Exposure to tobaco (current and ex-smokers)	17 (32.0)
Discoid lupus	4/52 (7.6)
Butterfly rash	21/52 (40.3)
Raynaud's phenomena	18/52 (34.6)
Oral ulcers	24/52 (46.1)
Arthritis	30/52 (57.6)
Convulsions	2/52 (3.8)
Psychosis	4/52 (7.6)
Serositis	10/53 (18.8)
Hemolytic anemia	9/52 (17.3)
Leukopenia	15/50 (30.0)
Thrombocytopenia	10/52 (19.2)
Glomerulonephritis	23/53 (43.3)
Anti-DNA	20/52 (38.4)
Anti-Ro/SS-A	21/51 (41.1)
Anti-La/SS-B	11/52 (21.1)
Anti-Sm	10/53 (18.8)
Anti-RNP	14/51 (27.4)
Direct Coombs	9/51 (17.6)
Anticardiolipin IgG	8/52 (15.3)
Anticardiolipin IgM	10/52 (19.2)
Lupus anticoagulant	7/51 (13.7)
Antiphospholip antibody syndrome	5/53 (9.4)
Antimalarial users	35/53 (66.0)
Methotrexate users	4/53 (7.5)
Leflunomide users	1/53 (1.8)
Mophetyl mycophenolate users	19/53 (35.8)
Azathioprin users	6/53 (11.3)
Cyclophosphanide users	0
Glucocorticoid users	16/53 (30.1)
Median SLEDAI (IQR)	2.0 (0-7.5)

IQR= interquartile rate;n=number

The prevalence of headache in this SLE population and comparison with controls is on

Table 2. None of the interviewed lupus patients had intractable headache.

Table 2- Prevalence of headache, degree of pain and quality of life measures in SLE sample and controls.

	Lupus - n (%) or central tendency	Controls - n (%) or central tendency	P
With headache (any)	37/53 (69.8)	35/53 (66.0)	0.67
Tensional headache	12/53 (22.6)	9/53 (16.9)	0.46
Cluster headache	1/53 (1.8)	0	
Migraine	25/53 (47.1)	22/53 (41.5)	0.55
Mean total headache VAS	6.3±2.23	6.35±1.91	0.96
Mean migraine VAS	6.5 (5-8)	7.0 (6-8)	0.46
Median MIDAS (IQR) (*)	12 (7-39)	15.0 (7.0-41.0)	0.84

*(*)- only in patients with migraine. VAS= visual analogic scale; MIDAS = Migraine Disability Assessment; SF-12= Short form healthy survey, SF-12= Short Form Healthy Survey-*12; SD=standard deviation.

The comparison of SF-12 mental and physical domains of SLE patients and controls with migraine showed p=0.14 for physical and p=0.96 for mental domain; with tension headache showed p=0.15 for physical and p=0.58 for mental domains.

The study of epidemiological, clinical, serological and treatment variables in SLE patients with and without any type of headache did not showed any differences (all p=ns).

Comparing the clinical and serological characteristics of SLE patients with and without migraine, the results of **Table 3** were found, where it is possible to see that patients with anti-Sm and with glomerulonephritis had a tendency to have less migraine.

Table 3- Comparison of epidemiological, clinical and serological data of systemic lupus erythematosus patients with and without migraine

	With migraine n=26	Without migraine n= 27	P
Mean age at disease onset	28.4±11.4	27.3±10.2	0.73
Discoid lupus	3/25 (12.0)	1/27 (3.7)	0.34
Butterfly rash	13/25 (52.0)	8/27 (29.6)	0.10
Photossensitivity	21/25 (84.0)	17/27 (62.9)	0.12
Raynaud's phenomena	11/25 (44.0)	7/27 (25.9)	0.13
Oral ulcers	13/25 (52.0)	11/27 (40.7)	0.79
Arthritis	15/25 (60.0)	15/27 (55.5)	0.74
Convulsions	0/25	2/27 (7.4)	0.49
Psychosis	1/25 (4.0)	3/27 (11.1)	0.61
Serositis	6/25 (24.0)	4/26 (15.3)	0.49
Hemolytic anemia	5/25 (20.0)	4/27 (14.8)	0.72
Leukopenia	5/24 (20.8)	10 /26 (38.4)	0.22
Thrombocytopenia	6/25 (24.0)	4/27 (14.8)	0.49
Glomerulonephritis	8/26 (30.7)	15/27 (55.5)	0.06
Anti-DNA	9/25 (37.5)	11/27 (40.7)	0.72
Anti-Ro/SS-A	9/25 (37.5)	12/27 (44.4)	0.53
Anti-La/SS-B	5/25 (20.0)	6/27 (29.6)	0.34
Anti-Sm	2/26 (7.6)	8/27 (31.8)	0.07
Anti-RNP	5/25 (20.0)	9/26 (34.6)	0.34
Anticardiolipin IgG	3/25 (12.0)	5/27 (18.5)	0.70
Anticardiolipin IgM	5/25 (20.0)	5/27 (18.5)	1.00
Lupus anticoagulant	2/24 (8.3.0)	5/27 (18.5)	0.42
Direct Coombs	4/25 (16.0)	5/26 (19.2)	1.00
Antiphospholip antibody syndrome	2/25 (8.0)	3/27 (11.1)	1.00
Antimalarial use	18/25 (72)	17/27 (62.9)	0.48
Methotrexate use	2/25 (8)	2/27 (7.4)	1.00
Azathioprin	4/25 (16)	2/27 (7.4)	0.41
Mophetil mycophenolate use	8/25 (32)	11/27 (40.7)	0.51
Glucocorticoid use	7/25 (28)	9/27 (33.3)	0.87
SLEDAI median- (IQR)	2.0 (0-6.0)	2.0 (0-11.7)	0.52
SF-12 mental domain- median (IQR)	42.0 (34.0-47.5)	46.9 (38.0-49.3)	0.07
SF-12 Physical domain -median (IQR)	40.5 (36.5-46.1)	45.4 (36.8-48.9)	0.20

SLEDAI= Systemic lupus erythematosus disease activity; IQR= interquartile rate; comn=number; SF= Short form health survey-12.

In the SLE sample with migraine, correlation studies showed that the MIDAS value had a modest correlation with disease activity (Rho=0.37; 95%CI=0.10-0.58; p=0.006). This did not happen with the VAS of pain (Rho= 0.17; p=0.22). Correlation of MIDAS value with quality of life showed a negative association with SF-12 mental domain (Rho=-0.45; 95%CI=0.65-0.20; p=0.0005) but not with SF-12 physical domain (Rho=- 0.05; p=0.71).

DISCUSSION

Our results have shown that SLE patients from our region do not have more headache than controls. The intensity of headache and migraine in both samples were also equal as well as the repercussions of migraine in quality of life measured by MIDAS. We also could not find any association of migraine with clinical, serological profile or used treatment, including the presence of antiphospholipid antibodies and Raynaud phenomena. However, a weak correlation of SLEDAI with MIDAS, the specific questionnaire for quality of life in migraine patients, was noted.

A study in 168 patients by Glanz et al. (18) showed a prevalence of headache of 62%, a number very similar to ours. Weder-Cisneros et al. (19) found a prevalence of 41% of headache in their 81 lupus patients, that was considered higher than the prevalence in their studied rheumatoid arthritis patients. The higher prevalence of headache in lupus is counteracted by several other studies including a metanalysis by Mitsikostas et al. (20) corroborating our findings.

Some authors (21) have linked the presence of antiphospholipid antibody with migraine, an association that was independent of any underlying disease and suggesting that glucocorticoids were highly effective in their treatment. They believed that these autoantibodies may cause migraine by promoting dysfunction of endothelial cells. Others could not prove such association (22-24). More recently antibodies to phosphatidylserine/prothrombin complex (aPS/PT) have been linked to migraine in patients with antiphospholipid antibody syndrome (25). We did not find any association with anticardiolipin (IgG and IgM) and lupus anticoagulant antibodies, but we did not study others antiphospholipid antibodies and this is a limitation in the present study. The inconsistency of observed results may be because several types of antiphospholipid antibodies may coexist in one patient and we usually measure only the most common. Different combinations or presence of less usual antiphospholipid antibodies may have different associations. Another explanation is the lack of standardization in tests used for these autoantibodies' detection.

Ainiala et al. (27), studying neuropsychiatric manifestations in 46 SLE patients from Finland, found that headache was the second most common symptom in this context with a prevalence of 54% (39% migraine and 15% tension) and noted an association of this symptom with concomitant use of steroid contradicting the previous suggestion that this drug could be used to treat them. In our sample glucocorticoids did not affect the presence of migraine. However, it is possible that a subtype of headache - the so called "lupus headache" described as a very severe, persistent, debilitating pain would have a different pathophysiological mechanism and treatment response (27). This intractable form of headache is quite uncommon, and no large series of such patients have been studied in isolation. They rather are mixed together with different types of headache not allowing their peculiar characteristics to appear. It is also possible that they result of the co-occurrence of depression and anxiety disorders, that may justify the poor response to treatment and chronicity (27).

Other association outlined in the literature is between migraine with Raynaud's phenomena (28,29). In both situations there is a role of vasomotor dysfunction in the pathogenesis (28). O'Keeffe et al (29) studying 41 hospital employees with Raynaud found a higher prevalence of migraine than in controls. Appenzeller et al. (30) found association of Raynaud's with migraine in lupus patients as well as an association with disease activity. In our sample we did not find association with either Raynaud's phenomena although the number of patients with Raynaud was almost twice in those with migraines than in those without it (44% vs 25%). The small sample number may be responsible for a type II statistical error. Nevertheless, Whitelaw et al (31) could not associate these two symptoms in their 85 SLE patients.

CONCLUSION

Summarizing, we could not prove that headaches were more common in lupus patients. We also could not associated the presence of headaches in general or migraine with a particular pattern of clinical or serological variables. In patients with migraine, a weak correlation of disease activity with quality of life was noted.

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ORIGINAL ARTICLE
TOPICS IN MEDICAL CLINIC
SYSTEMIC LUPUS ERYTHEMATOSUS AND TUBULAR LESIONS

LÚPUS ERITEMATOSO SISTÊMICO E LESÕES RENAIS TUBULARES

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Key words: Systemic lupus erythematosus, Renal lesion, Glomerulonephritis, Tubular lesion
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Abstract

Background: Glomerulonephritis is the most common manifestation of lupus nephritis. However, tubulointerstitial lesions are also seen. **Aim:** To analyze histological tubular alterations in renal biopsy of 32 lupus patients trying to verify its influence on treatment. **Material and Methods:** Biopsies were reviewed for glomerular lesions classification following the ISN/RPS 2003 classification. Tubulointerstitial histological evaluated findings were interstitial fibrosis/ tubular atrophy and presence of inflammatory infiltrates. Clinical, serological and renal function tests were collected from the charts, and patients were considered as responders, non-responders and partially responders to treatment after 12 months treatment. **Results:** Patients with interstitial fibrosis/ tubular atrophy had fewer chances to achieve total remission (p=0.02). Inflammatory infiltrates and the presence of anti dsDNA did not change the response rate (all p=ns) **Conclusion:** Interstitial fibrosis/ tubular atrophy are associated with poor response to nephritis treatment. **Endocrinol diabetes clin exp 2019 / 2081 - 2084.**

Resumo

Introdução: A glomerulonefrite é a manifestação mais comum da nefrite lúpica. No entanto, lesões túbulo intersticiais também são vistas. **Objetivo:** Analisar as alterações histológicas tubulares na biópsia renal de 32 pacientes lúpicos, buscando verificar sua influência no tratamento. **Material e Métodos:** As biópsias foram revisadas para classificação de lesões glomerulares seguindo a classificação ISN / RPS 2003. Os achados histopatológicos túbulo intersticiais analisados foram fibrose intersticial / atrofia tubular e presença de infiltrados inflamatórios. Testes clínicos, sorológicos e de função renal foram coletados dos prontuários, e os pacientes foram classificados como respondedores, não respondedores e parcialmente respondedores ao tratamento após 12 meses de tratamento. **Resultados:** Pacientes com fibrose intersticial / atrofia tubular tiveram menos chances de atingir remissão total (p = 0,02). Infiltrados inflamatórios e a presença de anti-dsDNA não alteraram a taxa de resposta (todos p = ns). Conclusão: A fibrose intersticial e atrofia tubular estão associadas com prejuízo na resposta ao tratamento da nefrite lúpica. **Endocrinol diabetes clin exp 2019 / 2081 - 2084.**

INTRODUCTION

Renal involvement in systemic lupus erythematosus (SLE) is one of most common and feared manifestation of this disease as it is related to high morbidity and increased rate of mortality (1). It has been estimated that almost half of lupus patients will develop kidney involvement and that 10% of them will go into renal failure (2,3,4). This type of manifestation is more common and more severe in afro descendants (1). Glomerulonephritis are the most studied renal involvement and it is, nowadays, classified according to the International Society of Nephrology (ISN)/ Renal Pathology Society (RPS) (5). Treatment and prognostic factors are associated with the predominant type of glomerulonephritis, being the class three and four the most severe forms (1).

Tubular lesions may also occur in SLE patients, usually associated with glomerular disease (1), but little attention has been paid to this kind of complication. Nevertheless they seen to be important prognostic markers of renal dysfunction (1,6).

In the present study we analyzed histological tubular alterations in renal biopsy of 32 SLE patients trying to verify its influence in the treatment response.

MATERIAL AND METHODS

This study was approved by the local Committee of Ethics in Research. Thirty-two renal biopsy specimens were reviewed for glomerular and tubular lesions. Included biopsies were from patients that fulfilled at least four classification criteria for SLE diagnosis (7), and were followed for at least two years after the diagnosis of renal involvement. They should also had completed the standard care treatment for lupus glomerulonephritis: cyclophosphamide (NYH scheme) or mophetyl mycophenolate for remission induction followed by azathioprine or mophetyl mycophenolate for remission maintenance (8). Patients under 16 years of age at diagnosis, associated Sjogren's syndrome, history of diabetes, with hypertension prior to the lupus renal glomerulonephritis and with biopsy material with less than ten glomeruli were excluded. Clinical, serological and renal function tests were collected from the charts, and patients were considered as responders, non-responders and partially responders to treatment after 12 months treatment. To be considered as responder patient should have had stabilization or improvement of renal function and reduction of proteinuria to less than 0.5 g / day and /or normal clearence or increase of only up to 10% without active sediment. To be considered as partially responders, they should show reduction of 50% of proteinuria with <3 g / day and / or normal clearance or with alteration of up to 10% of the previous value and / or normal sediment. Non-responders were those with deterioration of renal function after excluding causes such as sepsis, drugs, dehydration and renal vein thrombosis and / or increased proteinuria or non-reduction of proteinuria in order to fall into partial or total remission.

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A single examiner, blind to clinical data, reviewed all biopsies. Glomerular lesions classification followed the ISN/RPS 2003 classification (5). Tubulointerstitial histological evaluated findings were interstitial fibrosis/tubular atrophy and presence of inflammatory infiltrates.

Data was collected in frequency and contingency tables. Central tendency was expressed in mean and standard deviation (SD) in parametric sample and median and interquartile rate (IQR) in non-parametric samples. Comparison of clinical, serological data, glomerulonephritis type and treatment response according to tubular findings were done by Fisher and chi squared tests. The adopted significance was of 5%.

RESULTS

The studied sample characteristics is on **Table 1**.

Table 1- Epidemiological, clinical and serological data of 32 studied lupus patients.

Median age at disease onset – years (IQR)	26.0 (20.0-35.7)
Female gender	25/32 (78.1%)
Auto declared ethnic background	Afrosdescendants; 17/31 (54.8%) Caucasians: 13/31 (41.9%) Asiatic: 1/31 (3.2%)
Clinical manifestations	
Arthritis	23/32 (81.2%)
Oral ulcers	20/32 (62.5%)
Malar rash	17/32 (53.1%)
Discoid lesions	1/32 (3.1%)
Pleuritis	2/32 (6.2%)
Pericarditis	4/32 (12.5%)
Hemolytic anemia	4/32 (12.5%)
Leukopenia	5/32 (15.6%)
Lymphocytopenia	6/32 (18.7%)
Thrombocytopenia	4/32 (12.5%)
Convulsions	3/32 (9.3%)
Psychosis	3/32 (9.3%)
Serological profile	
Anti ds DNA	18/32 (56.2%)
Anti Ro/SS-A	8/32 (25%)
Anti La/SS-B	7/32 (21.8%)
Anti Sm	5/31 (15.6%)
Anti RNP	5/32 (16.1%)
Direct coombs	1/32 (3.1%)
Anticardiollipin IgG	3/32 (9.3%)
Anticardiolipin IGM	4/32 (12.5%)
Lupus anticoagulant	1/32 (3.1%)

Clinical and serological data was collected at time of renal biopsy. Clinical data was considered in a cumulative way and defined according to the American College of Rheumatology SLE classification criteria .
OBS- none of included patients filled Sidney criteria (9) for the presence of antiphospholipid antibody syndrome.

In this sample, the renal biopsy has revealed that 2/32(6.2%) had class 2; 6/32 (18.7%) had class 3; 15/32 (46.8%) had class 4; 8/32(25%) had class 5 and 1/32 had class 6 glomerulonephritis. In the tubules: 11/32 (34.3%) were normal, interstitial fibrosis/ tubular atrophy was present in 13/32 (40.6%), and 19/32 (59.3%) had inflammatory infiltrates. The renal function at biopsy time showed that the serum creatinine ranged from 0.5 to 3.2 mg/dL (median 1.1 mg/dL), renal clearance went from 24.7 to 152.1 mL/min (mean of 88 mL/min) and proteinuria went from 0.58 to 9.90 g/24h (median of 2.0 g/24h).

The comparison of glomerulonephritis classification, laboratorial and treatment response rate according to the presence of interstitial fibrosis/tubular atrophy is on **Table 2**. There it is possible to note that total remission was more common in those without such findings.

Table 2- Comparison of glomerulonephritis classification, laboratorial and treatment response rate according to the presence of insterstitial fibrosis/tubular atrophy in kidney biopsy of 32 lupus patients.

	With n=13	Without n=19	P
Median initial proteinuria (IQR) g/24h	2.15 (0.58-3.25)	3.24 (0.97-5.65)	0.36
Mean initial creatinine clearance (SD) mL/min	75.11±21.64	81.95±29.55	0.62
Total remission (n)	1/13 (7.6%)	9/19 (47.3%)	0.02 (*)
Partial remission (n)	9/13 (69.2%)	6/19 (31.5%)	0.07
Treatment failure (n)	3/13 (23.0%)	4/19 (21.0%)	1.00
Anti dsDNA (n)	8/13 (61.5%)	10/19 (52.6%)	0.61
Glomerulonephritis class (n)	II- 1/13 (7.6%) III-2/13 (15.3%) IV-4/13 (30.7%) V-5/13 (38.4%) VI-1/13 (7.6%)	II- 1/19 (5.2%0 III -4/19 (21.0%) IV -11/19 (57.8%) V- 3/19 (15.7%)	0.34

(*) OR=10.8- 95%CI =1.1 to 100.5; SD= standard deviation; IQR= interquartile rate; n=number.

The comparison of glomerulonephritis classification, laboratorial and treatment profile according to the presence of inflammatory infiltrate is on **Table 3**. This table shows that the two samples are statistically the same.

Table 3- Comparison of glomerulonephritis classification, laboratorial and treatment response rate according to the presence of inflammatory infiltrates in kidney biopsy of 32 lupus patients.

	With N=19	Without N=13	P
Mean initial proteinuria (SD) g/24h	2.58±1.90	4.20±3.59	0.24
Median initial creatinine clearance (IQR) mL/min	86.24(41.92-100.2)	85.26(60.07-140.9)	0.58
Total remission (n)	6/19 (31.5%)	1/13 (7.6%)	0.19
Partial remission (n)	9/19 (47.3%)	9/13 (69.1%)	0.28
Treatment failure (n)	4/19 (21.0%)	3/13 (23.0%)	1.0
Anti ds DNA (n)	12/39 (63.1%)	6/13 (46.1%)	0.34
Glomerulonephritis class (n)	II- 1/19 (5.2%)	II- 1/13 (7.6%)	0.63
	III- 3/19 (15.6%)	III- 3/13 (23.0%)	
	IV- 9/19 (47.3%)	IV- 6/13 (46.1%)	
	V- 6/19 (31.5%)	V- 2/13 15.3%	
	VI- 0	VI- 1/13 (7.6%)	

SD= standard deviation; IQR= interquartile rate; n=number.

DISCUSSION

Our results shows that only 34% of patients with glomerular involvement did not have tubular/interstitial damage. It also shows that the presence of fibrosis/atrophy but not inflammation was associated with poor treatment response. This finding is expected as established fibrosis, which follows the inflammation (1), is considered less responsive to treatment than inflammation.

Anti-dsDNA is the antibody considered the hallmark of lupus glomerulonephritis, participating in its pathophysiology (10). At present, we could not find any association this autoantibody with tubular/interstitial lesions. This was also detected in others studies (11,12). Rather, an anti cytoplasmatic antibody directed against vimentin has been observed (13). However, the exact meaning of this finding is unknown.

Some authors have pointed to the fact that glomerular and tubular lesions seems to follow distinct pathophysiologic pattern. Patients with purely glomerular or purely tubular injury have been found (1). While glomerular lesions are considered secondary to systemic autoimmunity (14, 15), local immunologic mechanism seems to play the main role in the tubular lesions (16). Nevertheless, the glomerular lesions may aggravated the tubular dysfunction. The glomerular efferent arteriole feeds the peritubular vascular bed; severe glomerular inflammation results in tubulointerstitial ischemia, damage and secondary inflammation (1). Proteins, such as albumin and transferrin that come into direct contact with proximal tubules because of glomerular integrity loss induce inflammation and fibrosis (17,18,19).

Recognition of tubulointerstitial fibrosis as a prognostic marker in lupus renal involvement may be important not only to prognosis but also to treatment. Experimental studies have suggested that mycophenolic acid, the metabolite of mycophenolate mophetil (MMF) may have anti-fibrotic effects on tubular cells not related to its immunomodulatory effects (20, 21). Therefore, it is possible to hope that early treatment with MMF in these patients may be beneficial to prevent the tubulointerstitial disease.

This study has several limitations; one of them is it small number of studied patients. Other is that interstitial fibrosis/tubular atrophy and inflammation were studied only on basis of its presence (a yes or no determination), and not graded according to their intensity. However, it does show the importance of evaluation of tubule interstitial involvement in lupus patients while analyzing the chances to answer to standard treatment.

CONCLUSION

We concluded that the presence of interstitial fibrosis/tubular atrophy are associated with worse response to treatment. Anti dsDNA does not predict tubular involvement in lupus nephritis.

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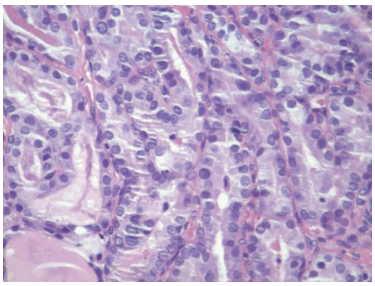
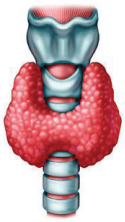
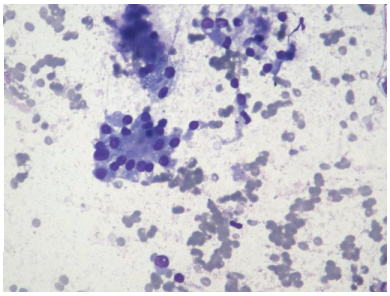
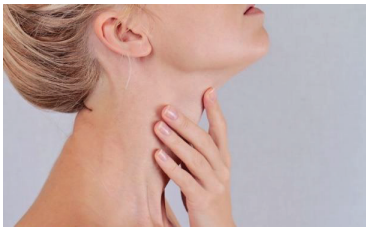
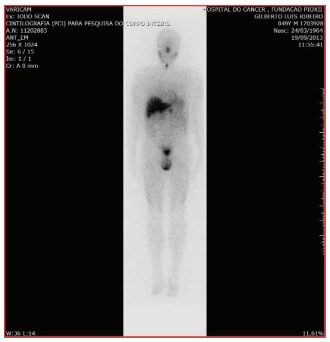
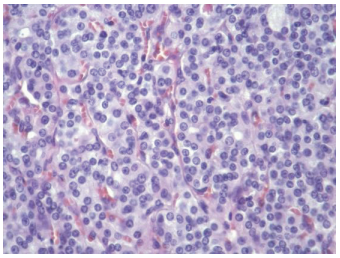






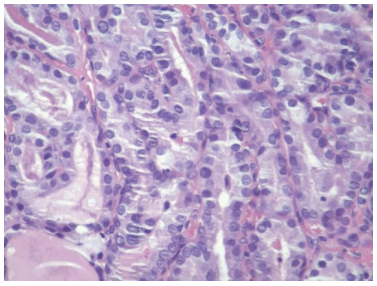


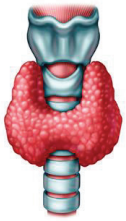


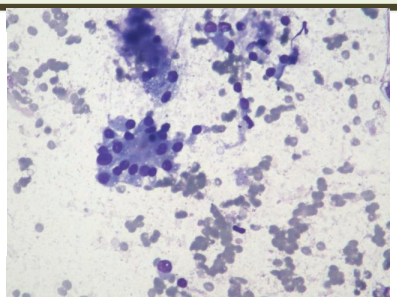


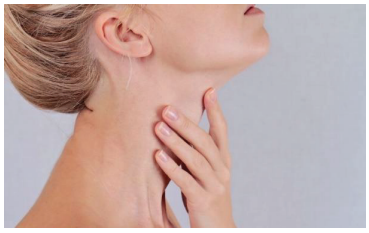
MÓDULO: Atualização em Câncer de Tireoide e Discussão de Casos Clínicos

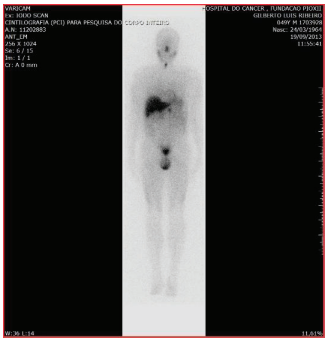
Dr Ricardo Ribeiro Gama
Serviço de Cirurgia de Cabeça e Pescoço do Hospital do Câncer de Barretos- São Paulo

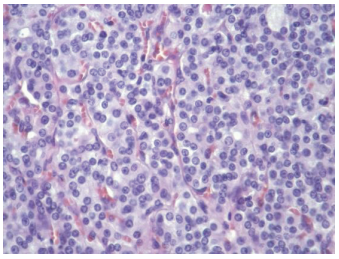












Epidemiologia

Nódulo palpável: **5%** em mulheres e **1%** em homens;

US alta resolução: prevalência de **19-68%** de nódulos;

Importância: excluir carcinoma (**7-15%** dos casos);

EUA 2009 - **37.200 novos casos** *vs* EUA 2014 – **63.000 novos casos**;

Aumento da incidência: apenas dos **tumores clinicamente ocultos?**;

2019 (USA): **terceiro** tumor mais comum com custo de **U$19-21 bilhões**;

Controvérsia clínica x carência de ensaios clínicos na área;

Objetivo: **minimizar** ***overtreatment*** sem comprometer tratamento e controle adequados em alto-risco;

Tratar **todos** os tumores malignos de tireoide: causa mais **dano** que benefício

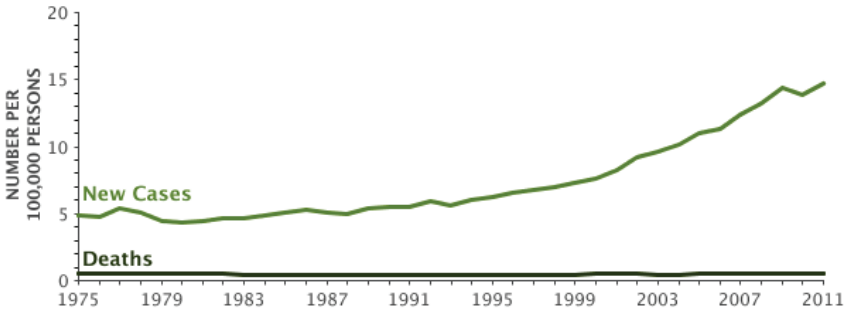
Epidemiologia - Mortalidade

Distribuição proporcional dos dez tipos de câncer mais incidentes estimados para 2018 por sexo, exceto pele não melanoma*

Localização Primária	Casos	%	Homens	Mulheres	Localização Primária	Casos	%
Próstata	68.220	31,7%			Mama Feminina	59.700	29,5%
Traqueia, Brônquio e Pulmão	18.740	8,7%			Cólon e Reto	18.980	9,4%
Cólon e Reto	17.380	8,1%			Colo do Útero	16.370	8,1%
Estômago	13.540	6,3%			Traqueia, Brônquio e Pulmão	12.530	6,2%
Cavidade Oral	11.200	5,2%			Glândula Tireoide	8.040	4,0%
Esôfago	8.240	3,8%			Estômago	7.750	3,8%
Bexiga	6.690	3,1%			Corpo do Útero	6.600	3,3%
Laringe	6.390	3,0%			Ovário	6.150	3,0%
Leucemias	5.940	2,8%			Sistema Nervoso Central	5.510	2,7%
Sistema Nervoso Central	5.810	2,7%			Leucemias	4.860	2,4%

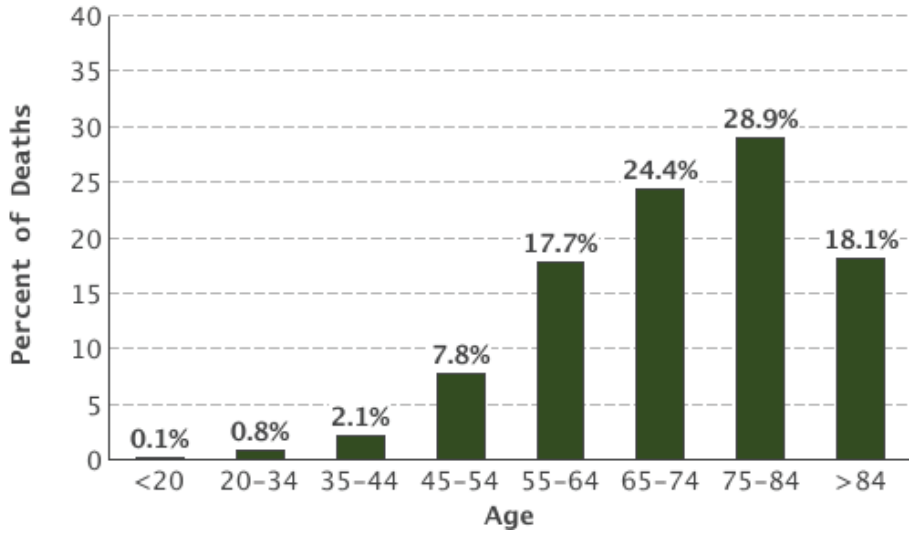
*Números arredondados para múltiplos de 10.

Fonte: INCA 2018



Fonte: SEER 2014

Epidemiologia - Mortalidade



Fonte: SEER 2014

Worldwide Thyroid-Cancer Epidemic? The Increasing Impact of Overdiagnosis

Salvatore Vaccarella, Ph.D., Silvia Franceschi, M.D., Freddie Bray, Ph.D., Christopher P. Wild, Ph.D., Martyn Plummer, Ph.D., and Luigino Dal Maso, Ph.D.

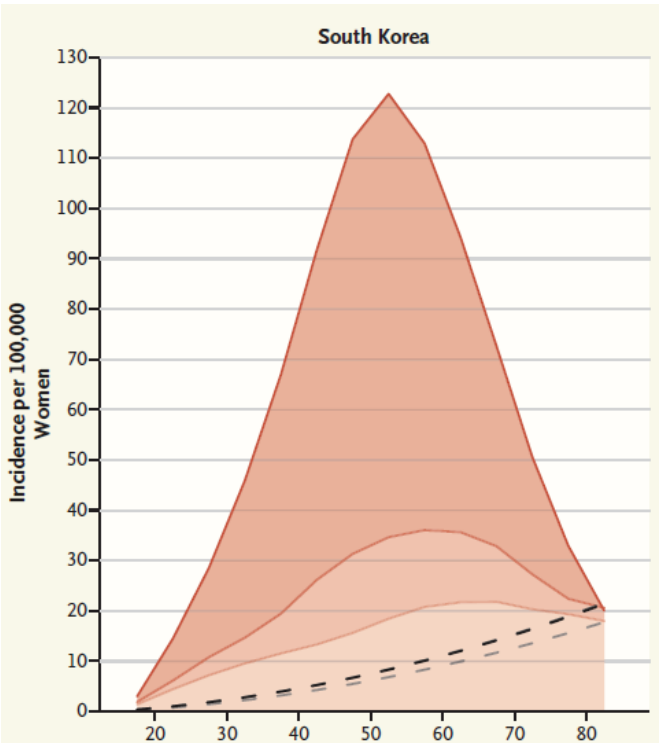
N ENGL J MED 375;7 NEJM.ORG AUGUST 18, 2016

#**Coréia do Sul**:**12.2** para **59.9** por 100.000 da década de 90 para anos 2000: **CÂNCER MAIS COMUM ENTRE MULHERES**, após *screening* populacional com US!

#Entre mulheres **50-59 anos**, **35 para 120** casos 100.000!

#**90%** dos novos casos de câncer de tireóide em mulheres entre 2003-2007 são ***OVERDIAGNOSIS!***

#Diagnóstico de grande reservatório de lesão maligna não letal, assintomática na tireoide em duas décadas: **470.000 casos entre mulheres e 90.000 casos entre homens** em 12 países desenvolvidos!



CAUSAS?

Exposure to flame retardant chemicals and occurrence and severity of papillary thyroid cancer: A case-control study Hoffman K

Exposição aos "flame retardants" (PBDE – polibrominato difenil éter) e PTC

5. Conclusion

With the incidence of thyroid cancer quickly increasing and little knowledge of what may be leading to this drastic increase (outside of 'over diagnosis'), understanding potential environmental factors contributing to thyroid cancer is critical. Our results suggest that exposure to BDE-209 and TCEP in the home environment may be associated with an increased risk of PTC. This is a critical concern, particularly as the

Environment International 107 (2017) 235–242

Associations between flame retardant applications in furniture foam, house dust levels, and residents' serum levels

Hammel SC *Environment International 107 (2017) 181–189*

4. Conclusion

Our results indicate that foam in sofas serves as an important source of flame retardants for exposure in humans, suggesting that removal of FRs from the foam or furniture pieces in the home could indeed reduce human exposure to these compounds. FR compounds were measured in

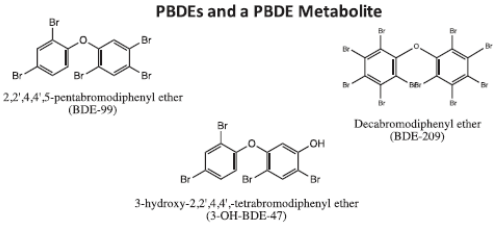
Do flame retardant chemicals increase the risk for thyroid dysregulation and cancer?

Hoffman K, Curr Opin Oncol. 2017 Jan;29(1):7-13

- Exposure to flame retardant chemicals, particularly newer-use flame retardants, is likely increasing.
- Evidence demonstrates that exposure to several different classes of flame retardant chemicals impacts thyroid hormone regulation and function.
- It remains unclear whether flame retardant exposure increases the risk of thyroid cancer; however, additional data are urgently needed as current evidence supports the hypothesis that flame retardant chemicals may impact the risk or severity of thyroid and other cancers.

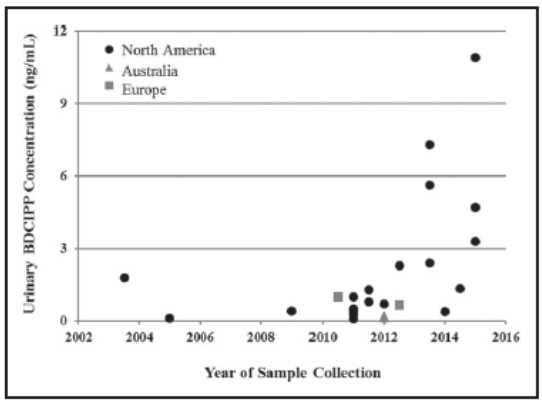
Thyroid Hormones

PBDEs and a PBDE Metabolite

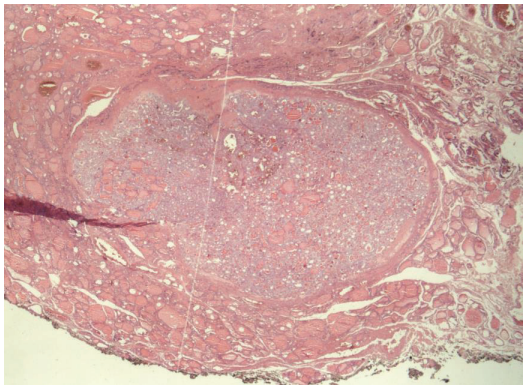


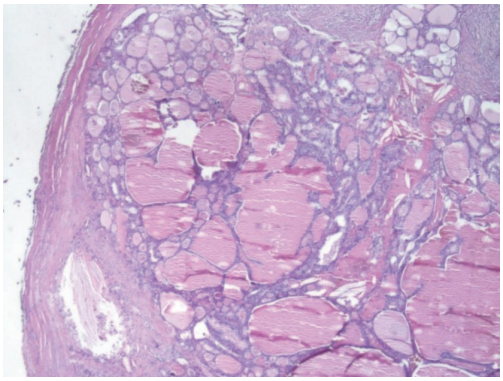
CONCLUSION

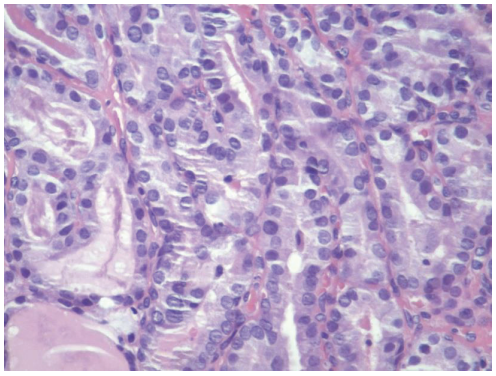
Although the past several years have seen significant advances in research related to PBDEs and thyroid regulation and disease, our understanding of their health impacts remains limited. Even less is known about the alternative FRs (e.g., PFRs and alternative BFRs), compounds for which exposure levels appear to be increasing. Given their structural similarities to PBDEs and thyroid hormones (i.e., alternative BFRs), and the limited number of animal studies suggesting alterations in circulating levels of thyroid hormones following exposure, more research is needed to understand the full extent of endocrine disruption for these compounds, and most importantly, mixtures of FRs that people are exposed to on a daily basis.



NFITP – "noninvasive folicular thyroid neoplasm with papillary-like nuclear features"







Fonte: Serviço de Patologia do HCB

Original Investigation

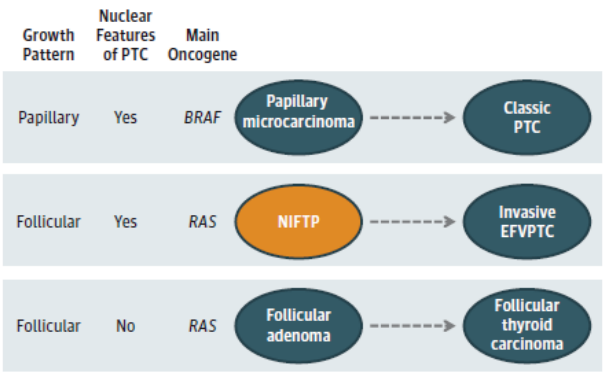
Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma

A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

Table. Summary of Follow-up Information for Patients in the Study Groups

Characteristic	Group 1 (Noninvasive EFVPTC) (n = 109)	Group 2 (Invasive EFVPTC) (n = 101)
Age, mean (range), y	45.9 (21-81)	42.8 (8-78)
Sex, No. (%)		
Female	91 (83)	71 (70)
Male	18 (17)	30 (30)
Tumor size, mean (range), cm	3.1 (1.1-9.0)	2.5 (0.6-5.5)
Extent of surgery		
Lobectomy	67	15
Total thyroidectomy	42	86
Follow-up, y		
Mean (range)	14.4 (10-26)	5.6 (1-18)
Median	13.0	3.5
Adverse events during follow-up, No. (%)	0	12 (12)

Figure 2. Putative Scheme of Thyroid Carcinogenesis



EFVPTC indicates encapsulated follicular variant of PTC; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma.

CONCLUSIONS AND RELEVANCE Thyroid tumors currently diagnosed as noninvasive EFVPTC have a very low risk of adverse outcome and should be termed NIFTP. This reclassification will affect a large population of patients worldwide and result in a significant reduction in psychological and clinical consequences associated with the diagnosis of cancer.

JAMA Oncol. doi:10.1001/jamaoncol.2016.0386
Published online April 14, 2016.

Características (NF-neoplasia folicular, ML- metástase nodal, EET-extensão ET, MD-met. dist.)	Carcinoma Papilífero Clássico (cPTC)	Carcinoma Papilífero Variante Folicular Encapsulado (NIFTP)	Carcinoma Papilífero Variante Folicular Invasor (FVPTC)	Carcinoma Folicular (FTC)	Adenoma Folicular
Epidemiologia	Em crescimento devido ao rastreamento ou uso indiscriminado do US	**Tumor híbrido (versão indolente que não é chamada de benigna)**	30% dos papilíferos; mais de 50% das NF à PAAF; 85% dos carcinomas de padrão folicular	Mantido ao longo das décadas	-------
Comportamento biológico	EET e metástase linfonodal são comuns	**Indolente como adenomas foliculares. Quando há IC ou IV comportam-se como FTC**	Menos MD que FTC mas mais que cPTC; menos EET e ML que cPTC mas mais que FTC. Comportam-se cPTC	MD e maior mortalidade	Indolente. Potencial para malignizar
Perfil molecular	BRAF é a mutação mais comum	**RAS é a mutação mais comum**	RAS é a mutação mais comum	RAS é a mutação mais comum	RAS é a mutação mais comum
Prognóstico	Excelente nos de baixo risco e na maioria de risco intermediário	**Comportamento benigno**	Prognóstico intermediário entre cPTC e FTC	Agressivo na dependência de fatores clínicos e anatomia-patológica	Benigno
Padrão à PAAF	Bethesda V ou VI	**Bethesda III ou IV**	Bethesda III,IV ou V(?)	Bethesda III ou IV	Bethesda III ou IV
Conduta diagnóstica	Tireoidectomia parcial ou total	**Tireoidectomia parcial**	Tireoidectomia parcial	Tireoidectomia parcial	Tireoidectomia parcial
Conduta terapêutica	Tireoidectomia parcial (baixo risco) ou total (intermediário ou alto risco)	**Tireoidectomia parcial**	Tireoidectomia parcial (baixo risco) ou total (intermediário ou alto risco)	Tireoidectomia total; parcial nos minimamente invasivos (?)	Tireoidectomia parcial

NFITP – "noninvasive folicular thyroid neoplasm with papillary-like nuclear features"

American Thyroid Association Guidelines on the Management of Thyroid Nodules and Differentiated Thyroid Cancer Task Force Review and Recommendation on the Proposed Renaming of Encapsulated Follicular Variant Papillary Thyroid Carcinoma Without Invasion to Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features

vasion. It therefore follows that there will be a small increase in false positives in the malignant category of The Bethesda System and a modest decrease in the risk of malignancy for the indeterminate subcategories (4–7). The proposed name change will also affect the performance of molecular tests when applied to patients with indeterminate cytology. For example, neoplasms harboring *RAS* mutations will likely have a lower positive predictive value (PPV) for malignancy, while nodules with no genetic mutation or a negative gene expression classifier will likely have a slightly higher negative predictive value (NPV). These effects will be dependent on the prevalence of NIFTP in a given population. Since NIFTP, like follicular adenoma, requires surgery for a definitive diagnosis, the changes in PPV and NPV of the molecular tests will not alter the requirement of surgical intervention for these patients. Potential frameworks for ad-

Haugen BR

THYROID
Volume 27, Number 4, 2017

The 2017 Bethesda System for Reporting Thyroid Cytopathology

Edmund S. Cibas, MD[a,*], Syed Z. Ali, MD[b]

Table 2 The 2017 Bethesda System for Reporting Thyroid Cytopathology: implied risk of malignancy and recommended clinical management.

Diagnostic category	Risk of malignancy if NIFTP ≠ CA (%)	Risk of malignancy if NIFTP = CA (%)	Usual management[a]
Nondiagnostic or Unsatisfactory	5-10	5-10	Repeat FNA with ultrasound guidance
Benign	0-3	0-3	Clinical and sonographic follow-up
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	6-18	~10-30	Repeat FNA, molecular testing, or lobectomy
Follicular Neoplasm or Suspicious for a Follicular Neoplasm	10-40	25-40	Molecular testing, lobectomy
Suspicious for Malignancy	45-60	50-75	Near-total thyroidectomy or lobectomy[b,c]

Thyroid. 2017 Nov;27(11):1341-1346.

Molecular Testing for Indeterminate Thyroid Nodules: Performance of the Afirma Gene Expression Classifier and ThyroSeq Panel

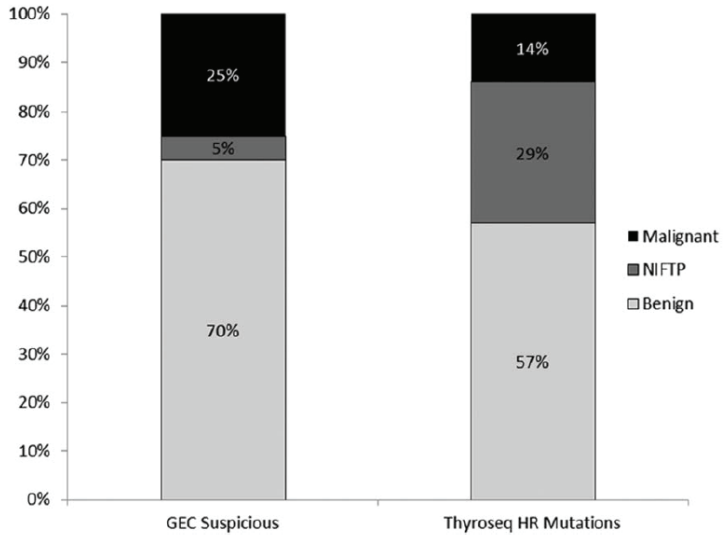


Figure 3. Comparison of results of surgically resected nodules for cases with a "positive" test result (either an Afirma gene expression classifier [GEC] "suspicious" result or high-risk [HR] mutations detected on ThyroSeq). NIFTP indicates noninvasive thyroid neoplasm with papillary-like nuclear features.

The findings of the current study support predictions that NIFTP decreases the risk of malignancy for a "positive" result for both the Afirma GEC and ThyroSeq,

Rachel C. Jug, MB.
Cancer Cytopathol. 2018 Apr 10.

Molecular Testing for Indeterminate Thyroid Nodules: Performance of the Afirma Gene Expression Classifier and ThyroSeq Panel

TABLE 5. Review of Current Studies Assessing PPV Within the Context of NIFTP for Molecular Testing

Cases in Literature With Suspicious Afirma GEC Results

	Benign	NIFTP	Malignant	PPV With NIFTP	PPV Without NIFTP	Absolute Decrease in PPV
Current study	58	4	21	30.1%	25.3%	4.8%
Hang 2017[13]	95	24	32	37.1%	21.2%	15.9%
Samulski 2016[14]	65	10	32	39.3%	29.9%	9.4%
Wong 2016[11]	41	14	8	34.9%	12.7%	22.2%

Cases in Literature With HR Mutations on ThyroSeq

	Benign	NIFTP	Malignant	PPV With NIFTP	PPV Without NIFTP	Absolute Decrease in PPV
Current study	8	4	2	42.9%	14.3%	28.6%
Valderrabano 2017[15]	19	3	11	42.4%	33.3%	9.1%

Abbreviations: GEC, gene expression classifier; HR, high risk; NIFTP, noninvasive thyroid neoplasm with papillary-like nuclear features; PPV, positive predictive value.

Rachel C. Jug, MB,
Cancer Cytopathol. 2018 Apr 10.

Estadiamento TNM – oitava edição

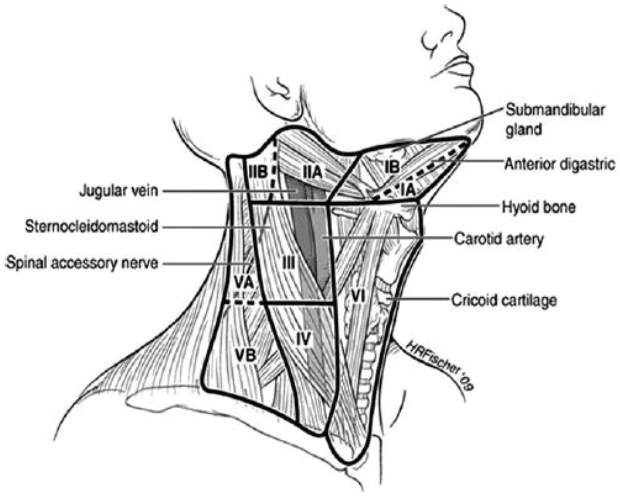
Principais modificações:
- **Mínima extensão extra-tireoidiana;**
- **Distinção entre N1a e N1b;**
- ***Cut-off* da idade para 55 anos**

TABLE 1. SEVENTH AND EIGHTH EDITION OF AJCC/UICC TNM STAGING SYSTEM OF DIFFERENTIATED THYROID CARCINOMA

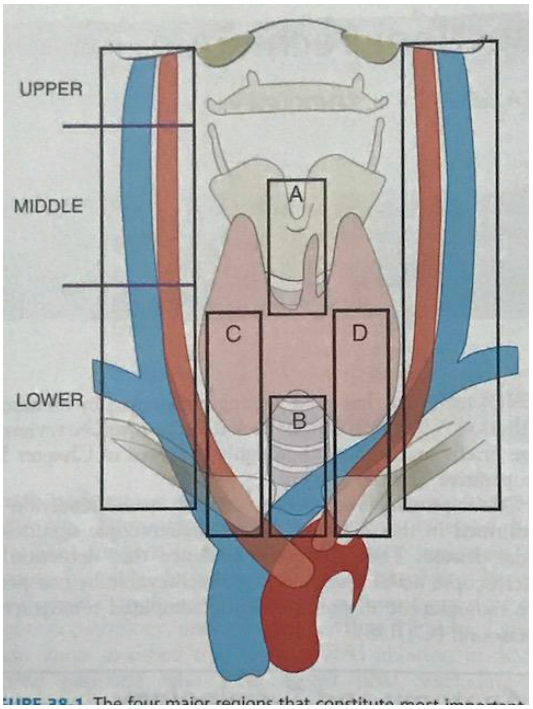
Seventh edition					*Eighth edition*				
	T	*N*	*M*	*Staging*		*T*	*N*	*M*	*Staging*
<45 years	Any T	Any N	M0	I	<55 years	Any T	Any N	M0	I
	Any T	Any N	M1	II		Any T	Any N	M1	II
≥45 years	T1	N0	M0	I	≥55 years	T1–2	N0/NX	M0	I
	T2	N0	M0	II		T1–2	N1	M0	II
	T3	N0	M0	III		T3	Any N	M0	II
	T1–3	N1a	M0	III		T4a	Any N	M0	III
	T4a	N0/N1a	M0	IVA		T4b	Any N	M0	IVA
	T1–4	N1b	M0	IVA		Any T	Any N	M1	IVB
	T4b	Any N	M0	IVB					
	Any T	Any N	M1	IVC					

AJCC/UICC, American Joint Committee on Cancer and International Union Against Cancer; TNM, tumor-node-metastasis.

Linfonodos cervicais

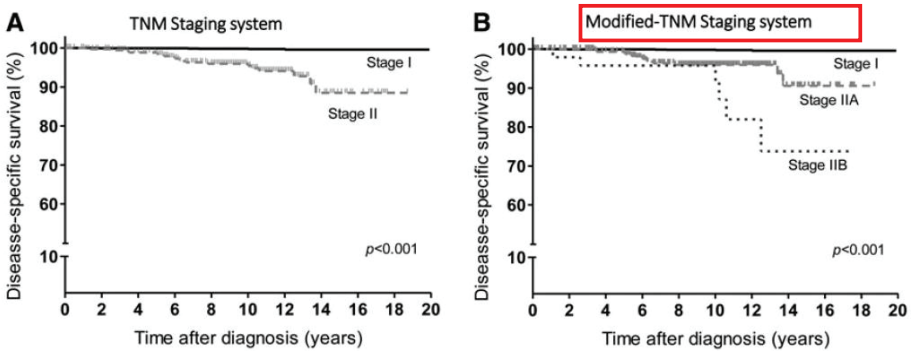


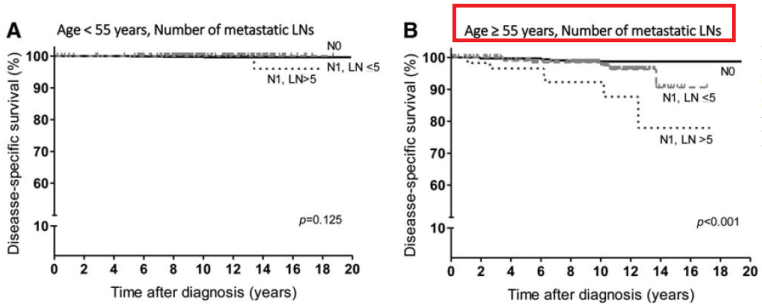
HAUGEN ET AL.
THYROID
Volume 26, Number 1, 2016



Randolph G. Surgery of the Thyroid and Parathyroid Glands, second edition, 2013

Prognostic Implication of N1b Classification in the Eighth Edition of the Tumor-Node-Metastasis Staging System of Differentiated Thyroid Cancer



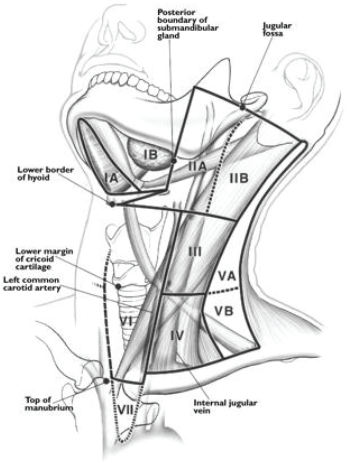


In conclusion, lateral LNM and number of metastatic LNs have a significant prognostic implication in patients with stage I/II DTC, especially in older patients (≥55 years). The study suggests that a modified TNM staging system including N1b would be more useful for the prediction of DSS in patients with DTC.

Kim M
THYROID
Volume 28, Number 4, 2018

Table 14. Characteristics According to the American Thyroid Association Risk Stratification System and AJCC/TNM Staging System That May Impact Postoperative Radioiodine Decision-Making

ATA risk Staging (TNM)	*Description*	*Body of evidence suggests RAI improves disease-specific survival?*	*Body of evidence suggests RAI improves disease-free survival?*	*Postsurgical RAI indicated?*
ATA low risk T1a N0,Nx M0,Mx	Tumor size ≤1 cm (uni-or multi-focal)	No	No	No
ATA low risk T1b,T2 N0, Nx M0,Mx	Tumor size >1–4 cm	No	Conflicting observational data	Not routine[b]—May be considered for patients with aggressive histology or vascular invasion (ATA intermediate risk).
ATA low to intermediate risk T3 N0,Nx M0,Mx	Tumor size >4 cm	Conflicting data	Conflicting observational data	Consider[b]—Need to consider presence of other adverse features. Advancing age may favor RAI use in some cases, but specific age and tumor size cutoffs subject to some uncertainty.[a]
ATA low to intermediate risk T3 N0,Nx M0,Mx	Microscopic ETE, any tumor size	No	Conflicting observational data	Consider[b]—Generally favored based on risk of recurrent disease. Smaller tumors with microscopic ETE may not require RAI.
ATA low to intermediate risk T1-3 N1a M0,Mx	Central compartment neck lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age (NTCTCSG Stage III)	Conflicting observational data	Consider[b]—Generally favored, due to somewhat higher risk of persistent or recurrent disease, especially with increasing number of large (>2–3 cm) or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.[a] However, there is insufficient data to mandate RAI use in patients with few (<5) microscopic nodal metastases in central compartment in absence of other adverse features.
ATA low to intermediate risk T1-3 N1b M0,Mx	Lateral neck or mediastinal lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age	Conflicting observational data	Consider[b]—Generally favored, due to higher risk of persistent or recurrent disease, especially with increasing number of macroscopic or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.[a]
ATA high risk T4 Any N Any M	Any size, gross ETE	Yes, observational data	Yes, observational data	Yes
ATA high risk M1 Any T Any N	Distant metastases	Yes, observational data	Yes, observational data	Yes



HAUGEN ET AL.
THYROID
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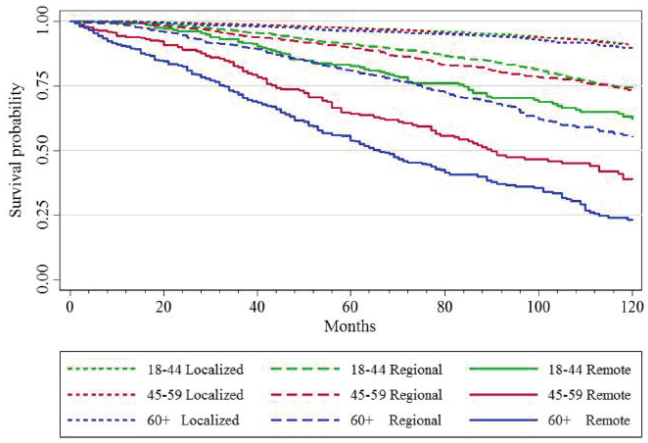
Idade como fator prognóstico. Por que 55 anos?

Age greater than 60 years portends a worse prognosis in patients with papillary thyroid cancer: should there be three age categories for staging?



Patients ≥60 years of age have worse DSS and DFS after a diagnosis of PTC, across all stages of disease.

Levamos em consideração **idade** isoladamente para indicar extensão do procedimento cirúrgico e iodoterapia?
Caso acima de 55 anos, T1/T2 - N0/NX, sem fatores prognósticos adversos e com tireoglobulina supressa pós-tireoidectomia total abaixo de 2,0 ng/mL, faríamos I131?

Lembrar que ATA não considera **IDADE** para estratificar risco!

Kauffmann *et al. BMC Cancer* (2018) 18:316

E a idade?

TABLE 11. ATA 2009 RISK STRATIFICATION SYSTEM WITH PROPOSED MODIFICATIONS

ATA low risk	Papillary thyroid cancer (with all of the following): • No local or distant metastases; • All macroscopic tumor has been resected • No tumor invasion of loco-regional tissues or structures • The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) • If ^{131}I is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan • No vascular invasion • Clinical N0 or ≤5 pathologic N1 micrometastases (<0.2 cm in largest dimension)[a] Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer[a] Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion[a] Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including *BRAF*^{V600E} mutated (if known)[a]
ATA intermediate risk	Microscopic invasion of tumor into the perithyroidal soft tissues RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) Papillary thyroid cancer with vascular invasion Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension[a] Multifocal papillary microcarcinoma with ETE and *BRAF*^{V600E} mutated (if known)[a]
ATA high risk	Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE) Incomplete tumor resection Distant metastases Postoperative serum thyroglobulin suggestive of distant metastases Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension[a] Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)[a]

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Gerando controvérsia...estimulando discussão...

#Tratamento do câncer de tireóide **mudou** ao longo dos anos!

#Diagnóstico de tumores subclínicos vem crescendo: **não pedir US sem fundamento clínico!**

#Nódulo no ultrassom: **não é sinônimo de PAAF!**

#Considerar **dados clínicos, de exame físico e ultrassonográficos em conjunto com Bethesda** para indicar cirurgia nos laudos citológicos de suspeição!

#Tireoidectomia **parcial** em contexto clínico específico é **preferível** que tireoidectomia **total**!

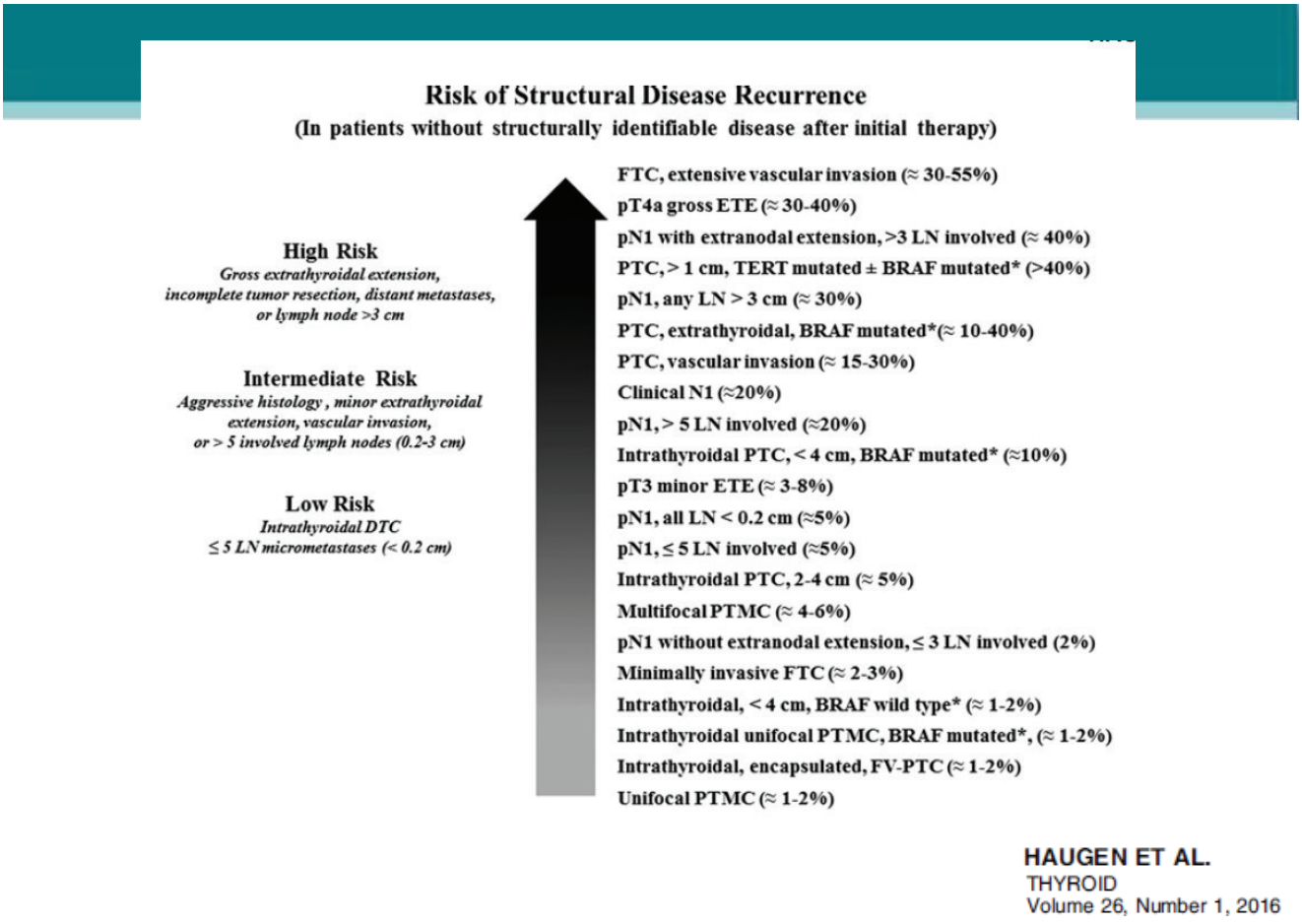
#Tireoidectomia **parcial diminui a morbidade** por reduzir complicações pós-operatórias (laringeo recurrente e paratireoides)!

#Iodoterapia **nem sempre** faz parte do tratamento do câncer de tireóide mas ainda **é a melhor forma de controlar doença sistêmica nos iodo-responsivos!**

#Sempre **estratificar** o paciente em seu grupo de risco e tratá-lo conforme o mesmo!

#Lembrar da **mudança da estratificação** do grupo conforme resposta ao tratamento inicial!

#**Terapia supressiva de TSH** beneficia apenas pacientes de **alto risco**!



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QUAL SERIA SUA CONDUTA?

MSB, sexo feminino, 60 anos submetida à tireoidectomia parcial esquerda por nódulo Bethesda IV. Patologia mostra carcinoma papilífero variante folicular com área focal de invasão da cápsula, com 8mm. Sua conduta seria:

a) totalizar tireoidectomia
b) totalizar tireoidectomia e realizar dose ablativa de I131
c) Totalizar tireoidectomia e realizar dose adjuvante de I131
d) Totalizar tireoidectomia, realizar dose adjuvante de I131 e manter TSH entre 0,5-0,1mU/L
e) Observação clínica mantendo TSH entre 0,5-2,0mU/L

Table 14. Characteristics According to the American Thyroid Association Risk Stratification System and AJCC/TNM Staging System That May Impact Postoperative Radioiodine Decision-Making

ATA risk Staging (TNM)	*Description*	*Body of evidence suggests RAI improves disease-specific survival?*	*Body of evidence suggests RAI improves disease-free survival?*	*Postsurgical RAI indicated?*
ATA low risk T1a N0,Nx M0,Mx	Tumor size ≤1 cm (uni-or multifocal)	No	No	No
ATA low risk T1b,T2 N0, Nx M0,Mx	Tumor size >1–4 cm	No	Conflicting observational data	Not routine[b]—May be considered for patients with aggressive histology or vascular invasion (ATA intermediate risk).
ATA low to intermediate risk T3 N0,Nx M0,Mx	Tumor size >4 cm	Conflicting data	Conflicting observational data	Consider[b]—Need to consider presence of other adverse features. Advancing age may favor RAI use in some cases, but specific age and tumor size cutoffs subject to some uncertainty.[a]
ATA low to intermediate risk T3 N0,Nx M0,Mx	Microscopic ETE, any tumor size	No	Conflicting observational data	Consider[b]—Generally favored based on risk of recurrent disease. Smaller tumors with microscopic ETE may not require RAI.
ATA low to intermediate risk T1-3 N1a M0,Mx	Central compartment neck lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age (NTCTCSG Stage III)	Conflicting observational data	Consider[b]—Generally favored, due to somewhat higher risk of persistent or recurrent disease, especially with increasing number of large (>2–3 cm) or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.[a] However, there is insufficient data to mandate RAI use in patients with few (<5) microscopic nodal metastases in central compartment in absence of other adverse features.
ATA low to intermediate risk T1-3 N1b M0,Mx	Lateral neck or mediastinal lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age	Conflicting observational data	Consider[b]—Generally favored, due to higher risk of persistent or recurrent disease, especially with increasing number of macroscopic or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.[a]
ATA high risk T4 Any N Any M	Any size, gross ETE	Yes, observational data	Yes, observational data	Yes
ATA high risk M1 Any T Any N	Distant metastases	Yes, observational data	Yes, observational data	Yes

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QUAL SERIA SUA CONDUTA?

LPA, 83 anos, com história de ICC por IAM há 6 meses. Em uso de clopidogrel e AAS. Incidentaloma de tireoide ao realizar doppler das carótidas. Nódulo de tireóide de 1cm, margens irregulares, com microcalcificações. PAAF mostra Bethesda VI. Risco cirúrgico elevado (ASA IV). Sua conduta seria:

a) Realizar tireoidectomia total
b) Realizar tireoidectomia total e dose adjuvante de I131
c) Realizar tireoidectomia total, dose adjuvante de I131 e manter TSH entre 0,5-0,1mU/L
d) Realizar tireoidectomia total, dose adjuvante de I131 e manter TSH entre 0,5-2,0mU/L
e) Observação clínica com ultrassom seriado

...já existem estratégias de observação em casos selecionados ...

Nonoperative management of low-risk differentiated thyroid carcinoma

Yasuhiro Ito[a,b] and Akira Miyauchi[a]

KEY POINTS

- Most low-risk PMCs do not grow or they grow very slowly, and immediate surgery for all PMCs may be an overtreatment.
- It is not too late to perform surgical treatment after the detection of progression signs such as size enlargement or novel appearance of lymph node metastasis during active observation.
- In contrast to clinical PTC, PMCs in older patients are less likely to progress than those in young or middle-aged patients.
- PMC in young patients is more likely to progress than PMCs in older patients, but since none of the patients who underwent surgery after the detection of progression signs showed recurrence, these patients can also be candidates for active observation.
- Whether TSH suppression with active observation is a better option than active observation alone remains an open question.

Table 1. Our treatment strategies for papillary thyroid microcarcinoma at Kuma Hospital, Kobe, Japan

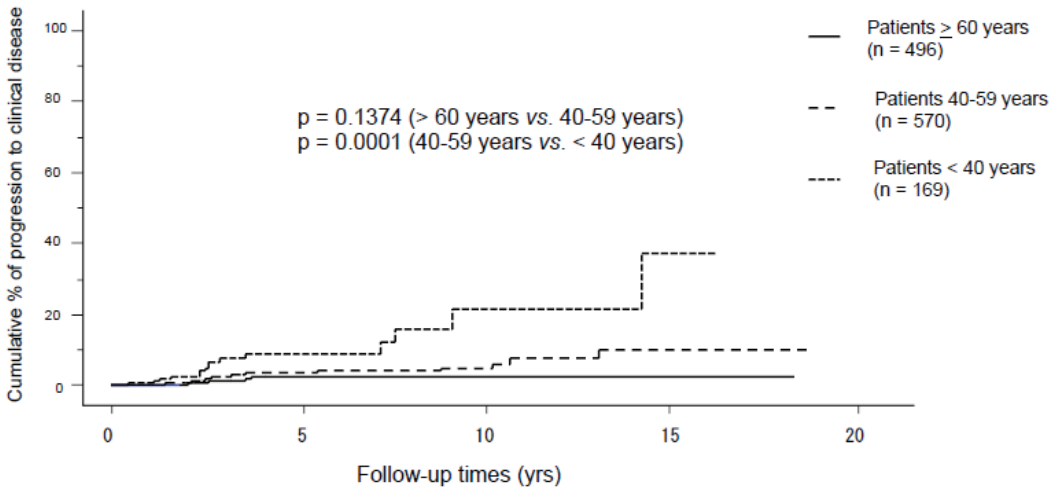
Low-risk PMC	Active observation. If patients prefer surgery, hemithyroidectomy (if solitary[a]) with ipsilateral level VI dissection without RAI ablation.
PMC with unsuitable features for observation	Hemithyroidectomy (if solitary[a]) with ipsilateral level VI dissection without RAI ablation.
PMC with high-risk features	Total thyroidectomy with level VI lymph node dissection.[b] RAI ablation may be considered.

Curr Opin Oncol. 2015 Jan; 27(1): 15–20.

Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation

Thyroid 2014;24:27-34.

#Cx imediata e obs clínica**: igualmente eficazes** na prevenção da morte por câncer de tireoide;
#1235 pacientes (média 75 meses): **3.5% progrediram, 0% morte;**
#Cuidado: **no *screening* sistemático e no tratamento de incidentalomas – observar** tumores de baixo risco tem uma tendência a ser **prioritário!**



QUAL SERIA SUA CONDUTA?

ADP, 54 anos, sexo masculino, submetido à tireoidectomia total por bócio multinodular. Laudo da patologia revela bócio colóide, associado com carcinoma papilífero clássico de 2,5cm em lobo direito, sem extensão extra-tireoidiana ou invasão vascular. Multifocalidade presente, com outro carcinoma papilífero clássico de 7mm em lobo esquerdo. Presença de dois linfonodos peritireoidanos comprometidos por carcinoma papilífero. Tireoglobulina supressa com 90 dias de pós-operatório é de 0,2 ng/mL. Sua conduta seria:

a) Realizar dose ablativa de I131
b) Realizar dose adjuvante de I131 e manter TSH entre 0,5-0,1mU/L
c) Realizar dose adjuvante de I131 e manter TSH entre 0,5-2,0mU/L
d) Observação clínica mantendo TSH entre 0,5-0,1mU/L
e) Observação clínica mantendo TSH entre 0,5-2,0mU/L

TABLE 14. CHARACTERISTICS ACCORDING TO THE AMERICAN THYROID ASSOCIATION RISK STRATIFICATION SYSTEM AND AJCC/TNM STAGING SYSTEM THAT MAY IMPACT POSTOPERATIVE RADIOIODINE DECISION-MAKING

ATA risk Staging (TNM)	*Description*	*Body of evidence suggests RAI improves disease-specific survival?*	*Body of evidence suggests RAI improves disease-free survival?*	*Postsurgical RAI indicated?*
ATA low risk T1a N0,Nx M0,Mx	Tumor size ≤1 cm (uni-or multifocal)	No	No	No
ATA low risk T1b,T2 N0, Nx M0,Mx	Tumor size >1–4 cm	No	Conflicting observational data	Not routine[b]—May be considered for patients with aggressive histology or vascular invasion (ATA intermediate risk).
ATA low to intermediate risk T3 N0,Nx M0,Mx	Tumor size >4 cm	Conflicting data	Conflicting observational data	Consider[b]—Need to consider presence of other adverse features. Advancing age may favor RAI use in some cases, but specific age and tumor size cutoffs subject to some uncertainty.[a]
ATA low to intermediate risk T3 N0,Nx M0,Mx	Microscopic ETE, any tumor size	No	Conflicting observational data	Consider[b]—Generally favored based on risk of recurrent disease. Smaller tumors with microscopic ETE may not require RAI.
ATA low to intermediate risk T1-3 N1a M0,Mx	Central compartment neck lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age (NTCTCSG Stage III)	Conflicting observational data	Consider[b]—Generally favored, due to somewhat higher risk of persistent or recurrent disease, especially with increasing number of large (>2–3 cm) or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.[a] However, there is insufficient data to mandate RAI use in patients with few (<5) microscopic nodal metastases in central compartment in absence of other adverse features.
ATA low to intermediate risk T1-3 N1b M0,Mx	Lateral neck or mediastinal lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age	Conflicting observational data	Consider[b]—Generally favored, due to higher risk of persistent or recurrent disease, especially with increasing number of macroscopic or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.[a]
ATA high risk T4 Any N Any M	Any size, gross ETE	Yes, observational data	Yes, observational data	Yes
ATA high risk M1 Any T Any N	Distant metastases	Yes, observational data	Yes, observational data	Yes

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QUAL SERIA SUA CONDUTA?

GPD, 33 anos, sexo feminino, submetida à tireoidectomia parcial direita por nódulo Bethesda V. Laudo da patologia revela carcinoma papilífero clássico de 1cm, intra-tireoidiano, BRAF mutado. Sua conduta seria:

a) Observação clínica
b) Realizar tireoidectomia total e decidir sobre I131 na dependência do valor de tireoglobulina no pós-operatório
c) Realizar tireoidectomia total seguida de dose adjuvante de I131 e manter TSH entre 0,5-0,1mU/L
d) Realizar tireoidectomia total seguida de dose adjuvante de I131 e manter TSH entre 0,5-2,0mU/L
e) Realizar tireoidectomia total seguida de dose adjuvante de I131 e manter TSH abaixo de 0,1mU/L

TABLE 14. CHARACTERISTICS ACCORDING TO THE AMERICAN THYROID ASSOCIATION RISK STRATIFICATION SYSTEM AND AJCC/TNM STAGING SYSTEM THAT MAY IMPACT POSTOPERATIVE RADIOIODINE DECISION-MAKING

ATA risk Staging (TNM)	*Description*	*Body of evidence suggests RAI improves disease-specific survival?*	*Body of evidence suggests RAI improves disease-free survival?*	*Postsurgical RAI indicated?*
ATA low risk T1a N0,Nx M0,Mx	Tumor size ≤1 cm (uni-or multi-focal)	No	No	No
ATA low risk T1b,T2 N0, Nx M0,Mx	Tumor size >1–4 cm	No	Conflicting observational data	Not routine[b]—May be considered for patients with aggressive histology or vascular invasion (ATA intermediate risk).
ATA low to intermediate risk T3 N0,Nx M0,Mx	Tumor size >4 cm	Conflicting data	Conflicting observational data	Consider[b]—Need to consider presence of other adverse features. Advancing age may favor RAI use in some cases, but specific age and tumor size cutoffs subject to some uncertainty.[a]
ATA low to intermediate risk T3 N0,Nx M0,Mx	Microscopic ETE, any tumor size	No	Conflicting observational data	Consider[b]—Generally favored based on risk of recurrent disease. Smaller tumors with microscopic ETE may not require RAI.
ATA low to intermediate risk T1-3 N1a M0,Mx	Central compartment neck lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age (NTCTCSG Stage III)	Conflicting observational data	Consider[b]—Generally favored, due to somewhat higher risk of persistent or recurrent disease, especially with increasing number of large (>2–3 cm) or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.[a] However, there is insufficient data to mandate RAI use in patients with few (<5) microscopic nodal metastases in central compartment in absence of other adverse features.
ATA low to intermediate risk T1-3 N1b M0,Mx	Lateral neck or mediastinal lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age	Conflicting observational data	Consider[b]—Generally favored, due to higher risk of persistent or recurrent disease, especially with increasing number of macroscopic or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.[a]
ATA high risk T4 Any N Any M	Any size, gross ETE	Yes, observational data	Yes, observational data	Yes
ATA high risk M1 Any T Any N	Distant metastases	Yes, observational data	Yes, observational data	Yes

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BRAF mutado: baixo risco ou intermediário na dependência de outros fatores?

(C) While not routinely recommended for initial postoperative risk stratification in DTC, the mutational status of *BRAF*, and potentially other mutations such as *TERT*, have the potential to refine risk estimates when interpreted in the context of other clinico-pathologic risk factors.

(Weak recommendation, Moderate-quality evidence)

QUAL SERIA SUA CONDUTA?

OS, 28 anos, submetida à tireoidectomia total por nódulo Bethesda V de 1.5cm no lobo direito e outros nódulos (não puncionados) no lobo esquerdo, menores de 1cm. Laudo da patologia mostrou carcinoma papilífero variante folicular de 1.5cm com extensão extra-tireoidiana mínima (gordura peri-tireoidiana). Tireoglobulina 90 dias após a cirurgia é de 0,5ng/mL. Sua conduta seria:

a) Observação clínica e manter TSH entre 0,5-0,1mU/L
b) Observação clínica e manter TSH entre 0,5-2,0mU/L
c) Realizar dose ablativa de I131 e manter TSH entre 0,5-2,0mU/L
d) Realizar dose adjuvante de I131 e manter TSH entre 0,5-0,1mU/L
e) Realizar dose adjuvante de I131 e manter TSH entre 0,5-2,0mU/L

TABLE 14. CHARACTERISTICS ACCORDING TO THE AMERICAN THYROID ASSOCIATION RISK STRATIFICATION SYSTEM AND AJCC/TNM STAGING SYSTEM THAT MAY IMPACT POSTOPERATIVE RADIOIODINE DECISION-MAKING

ATA risk Staging (TNM)	*Description*	*Body of evidence suggests RAI improves disease-specific survival?*	*Body of evidence suggests RAI improves disease-free survival?*	*Postsurgical RAI indicated?*
ATA low risk T1a N0,Nx M0,Mx	Tumor size ≤1 cm (uni-or multi-focal)	No	No	No
ATA low risk T1b,T2 N0, Nx M0,Mx	Tumor size >1–4 cm	No	Conflicting observational data	Not routine[b]—May be considered for patients with aggressive histology or vascular invasion (ATA intermediate risk).
ATA low to intermediate risk T3 N0,Nx M0,Mx	Tumor size >4 cm	Conflicting data	Conflicting observational data	Consider[b]—Need to consider presence of other adverse features. Advancing age may favor RAI use in some cases, but specific age and tumor size cutoffs subject to some uncertainty.[a]
ATA low to intermediate risk T3 N0,Nx M0,Mx	Microscopic ETE, any tumor size	No	Conflicting observational data	Consider[b]—Generally favored based on risk of recurrent disease. Smaller tumors with microscopic ETE may not require RAI.
ATA low to intermediate risk T1-3 N1a M0,Mx	Central compartment neck lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age (NTCTCSG Stage III)	Conflicting observational data	Consider[b]—Generally favored, due to somewhat higher risk of persistent or recurrent disease, especially with increasing number of large (>2–3 cm) or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.[a] However, there is insufficient data to mandate RAI use in patients with few (<5) microscopic nodal metastases in central compartment in absence of other adverse features.
ATA low to intermediate risk T1-3 N1b M0,Mx	Lateral neck or mediastinal lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age	Conflicting observational data	Consider[b]—Generally favored, due to higher risk of persistent or recurrent disease, especially with increasing number of macroscopic or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.[a]
ATA high risk T4 Any N Any M	Any size, gross ETE	Yes, observational data	Yes, observational data	Yes
ATA high risk M1 Any T Any N	Distant metastases	Yes, observational data	Yes, observational data	Yes

Extensão extra-tireoidiana mínima **já não é mais** considerada fator prognóstico no novo TNM!

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QUAL SERIA SUA CONDUTA?

EAF, 73 anos, sexo feminino, com história de câncer renal metastático em tratamento com sunitinibe. PET-CT de controle revela nódulo de tireoide com SUV de 17. Ultrassom da tireoide mostra nódulo em lobo direito de 2cm, hipoecoico, margens regulares. PAAF: Bethesda IV. Eutireoidiana. Sua conduta seria:

a) Observação clínica com novo ultrassom em 6 meses
b) Repetir PAAF
c) Realizar teste molecular ("*rule out test*") e operar apenas se resultado for suspeito
d) Realizar tireoidectomia parcial diagnóstica
e) Realizar tireoidectomia total

QUAL SERIA SUA CONDUTA?

LPT, 28 anos, sexo masculino, em uso de Puran T4 100mcg, com nódulo de 3cm, hiperecóico, margens regulares, único. PAAF: Bethesda III. Sua conduta seria:

a) Observação clínica com novo ultrassom em 6 meses
b) Repetir PAAF
c) Realizar teste molecular ("*rule out test*") e operar apenas se resultado for suspeito
d) Realizar tireoidectomia parcial diagnóstica
e) Realizar tireoidectomia total

QUAL SERIA SUA CONDUTA?

PS, 60 anos, sexo masculino, submetido à tireoidectomia total. Patologia mostra carcinoma de células de Hurtle com extensa invasão da cápsula e vascular, com 4cm. Linfadenectomia recurrencial com 10 linfonodos metastáticos, sem extensão extra-capsular. Invasão da musculatura infra-hioidea. Margens livres. Tireoglobuina supressa com 90 dias de pós-operatório é de 5ng/mL. Sua conduta seria:

a) Observação clínica com nova tireoglobulina em 6 meses, mantendo TSH entre 0,5-0,1mU/L
b) Dose ablativa de I131 e manter TSH entre 0,5-2,0mU/L
c) Dose adjuvante de I131 e manter TSH entre 0,5-2,0mU/L
d) Dose adjuvante de I131 e manter TSH entre 0,5-0,1mU/L
e) Dose adjuvante de I131 e manter TSH abaixo de 0,1mU/L

TABLE 14. CHARACTERISTICS ACCORDING TO THE AMERICAN THYROID ASSOCIATION RISK STRATIFICATION SYSTEM AND AJCC/TNM STAGING SYSTEM THAT MAY IMPACT POSTOPERATIVE RADIOIODINE DECISION-MAKING

ATA risk Staging (TNM)	*Description*	*Body of evidence suggests RAI improves disease-specific survival?*	*Body of evidence suggests RAI improves disease-free survival?*	*Postsurgical RAI indicated?*
ATA low risk T1a N0,Nx M0,Mx	Tumor size ≤1 cm (uni-or multi-focal)	No	No	No
ATA low risk T1b,T2 N0, Nx M0,Mx	Tumor size >1–4 cm	No	Conflicting observational data	Not routine[b]—May be considered for patients with aggressive histology or vascular invasion (ATA intermediate risk).
ATA low to intermediate risk T3 N0,Nx M0,Mx	Tumor size >4 cm	Conflicting data	Conflicting observational data	Consider[b]—Need to consider presence of other adverse features. Advancing age may favor RAI use in some cases, but specific age and tumor size cutoffs subject to some uncertainty.[a]
ATA low to intermediate risk T3 N0,Nx M0,Mx	Microscopic ETE, any tumor size	No	Conflicting observational data	Consider[b]—Generally favored based on risk of recurrent disease. Smaller tumors with microscopic ETE may not require RAI.
ATA low to intermediate risk T1-3 N1a M0,Mx	Central compartment neck lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age (NTCTCSG Stage III)	Conflicting observational data	Consider[b]—Generally favored, due to somewhat higher risk of persistent or recurrent disease, especially with increasing number of large (>2–3 cm) or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.[a] However, there is insufficient data to mandate RAI use in patients with few (<5) microscopic nodal metastases in central compartment in absence of other adverse features.
ATA low to intermediate risk T1-3 N1b M0,Mx	Lateral neck or mediastinal lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age	Conflicting observational data	Consider[b]—Generally favored, due to higher risk of persistent or recurrent disease, especially with increasing number of macroscopic or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.[a]
ATA high risk T4 Any N Any M	Any size, gross ETE	Yes, observational data	Yes, observational data	Yes
ATA high risk M1 Any T Any N	Distant metastases	Yes, observational data	Yes, observational data	Yes

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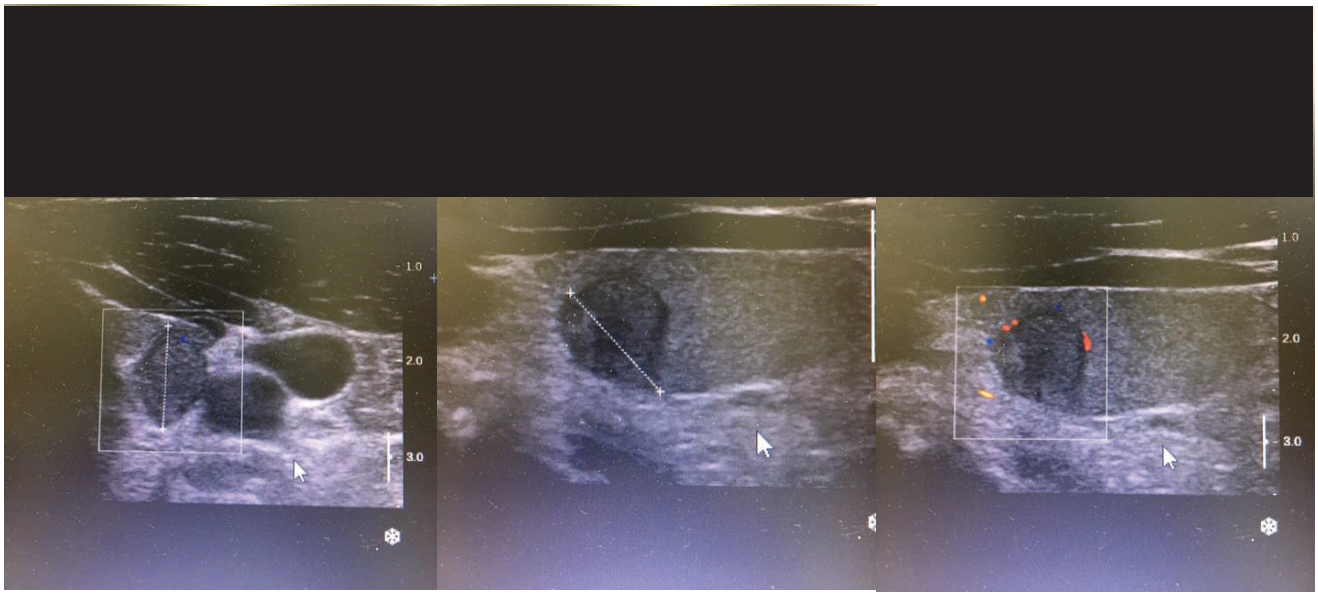
CASO CLÍNICO 1

JPR, **sexo masculino, 65 anos**, com **incidentaloma de tireoide** ao realizar US doppler de carótidas. História de DM2, IAM. Faz uso de somalgin, sinvastatina e Galvusmet. Sem nódulo palpável.TSH:**2.91**, T4 livre:1.15

US de tireoide: Formação nodular heterogênea, predominantemente **hipoecóica,** de **limites parcialmente precisos e lobulados**, no polo superior à esquerda, com **1.3cm** no maior diâmetro, com componente hipovascular periférico. Ausência de linfonodomegalia cervical.

CONDUTA:
1- PUNCIONAR OU OBSERVAR?

CASO CLÍNICO 1



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CONDUTA BASEADA NO LAUDO ORIGINAL:
Nódulo de suspeita intermediária (10-20%)

PUNCIONAR OU OBSERVAR?

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CONDUTA BASEADA NO LAUDO ORIGINAL:
Nódulo de suspeita intermediária (10-20%): puncionar quando maior que 1 cm

RESPOSTA:
PUNÇÃO GUIADA POR US DO NÓDULO

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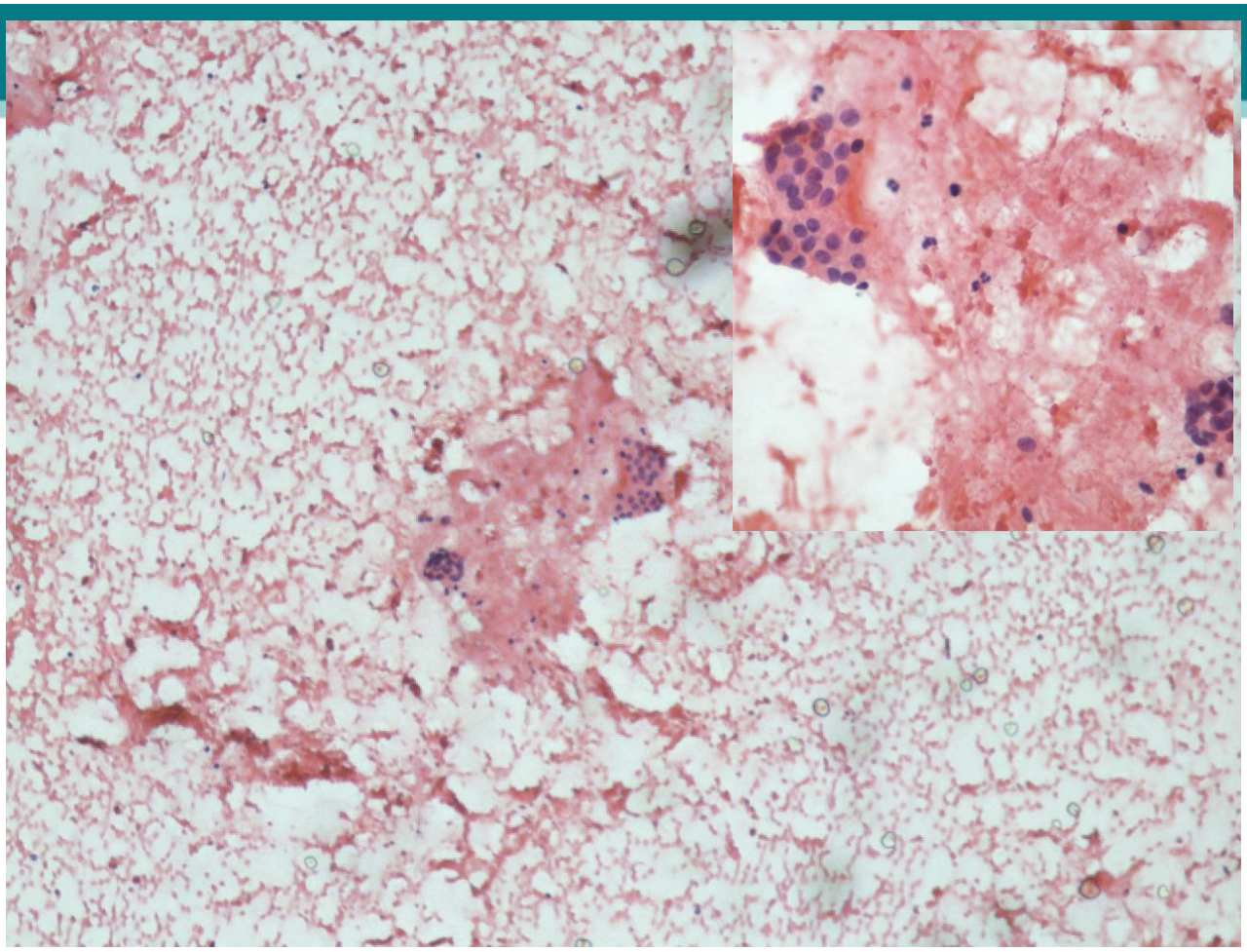
Punção do nódulo A:
Aspectos citológicos com atipia de significado indeterminado (Bethesda III)
Bethesda III: 10-15% de malignidade

CONDUTA
Repuncionar? Teste molecular ("*rule out test*")? Tireoidectomia parcial esquerda? Tireoidectomia total?



2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

(A) For nodules with AUS/FLUS cytology, after consideration of worrisome clinical and sonographic features, investigations such as repeat FNA or molecular testing may be used to supplement malignancy risk assessment in lieu of proceeding directly with a strategy of either surveillance or diagnostic surgery. Informed patient preference and feasibility should be considered in clinical decision-making. (**Weak recommendation, Moderate-quality evidence**)

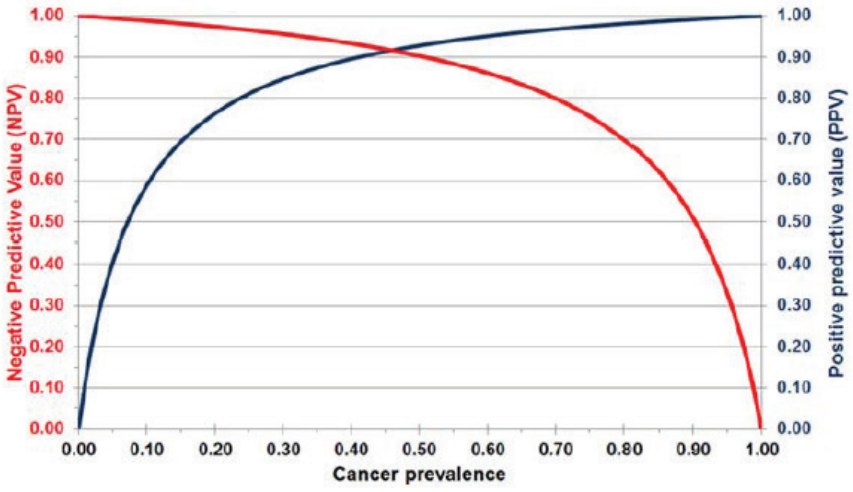
(A) Diagnostic surgical excision is the long-established standard of care for the management of follicular neoplasm/suspicious for follicular neoplasm (FN/SFN) cytology nodules. However, after consideration of clinical and sonographic features, molecular testing may be used to supplement malignancy risk assessment data, in lieu of proceeding directly with surgery. Informed patient preference and feasibility should be considered in clinical decision-making. (**Weak recommendation, Moderate-quality evidence**)

(B) After consideration of clinical and sonographic features, mutational testing for *BRAF* or the 7-gene mutation marker panel (*BRAF, RAS, RET/PTC, PAX8/PPARγ*) may be considered in nodules with SUSP cytology if such data would be expected to alter surgical decision-making. (**Weak recommendation, Moderate-quality evidence**)

Highly Accurate Diagnosis of Cancer in Thyroid Nodules With Follicular Neoplasm/Suspicious for a Follicular Neoplasm Cytology by ThyroSeq v2 Next-Generation Sequencing Assay

Cancer 2014;120:3627-34

Teste molecular: quanto maior a prevalência de câncer menor será o valor preditivo negativo e maior será o valor preditivo positivo...



VPN: proporção de pacientes com teste negativo que não têm a doença e depende da **PREVALÊNCIA** da doença

TESTES MOLECULARES

Utilizado para **descartar malignidade!** ***("rule-out test")***

Indicações:

***sem características de alto risco (história clínica, US, exame físico);**

***Bethesda III ou IV;**

***usualmente para nódulos menores de 4cm**: geralmente os maiores não-colóide são cirúrgicos;

***baixa prevalência de câncer institucional nos suspeitos ao PAAF**
(VPN para Bethesda III e IV: **95% - para uma prevalência de malignidade <=25%);**

***se paciente deseja observar caso negativo** (guideline X prática clínica de tratamento individualizado)

Conduta:
***Se negativo: observar;**

***Se positivo: usualmente lobectomia diagnóstica** ... muitos "positivos" serão **Neoplasia folicular não-invasora com característica nuclear papilífera-símile ou adenomas**

CASO CLÍNICO 1

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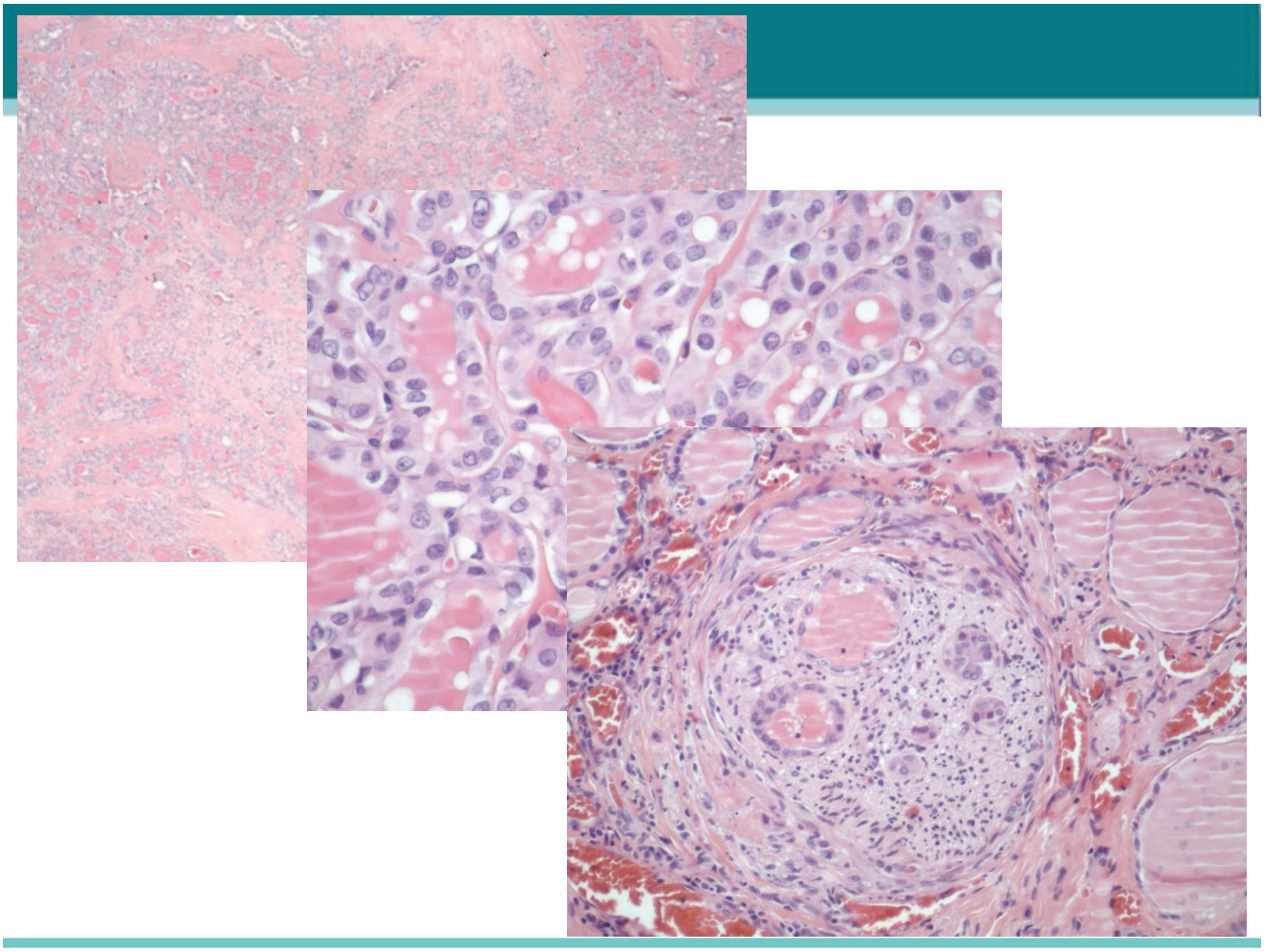
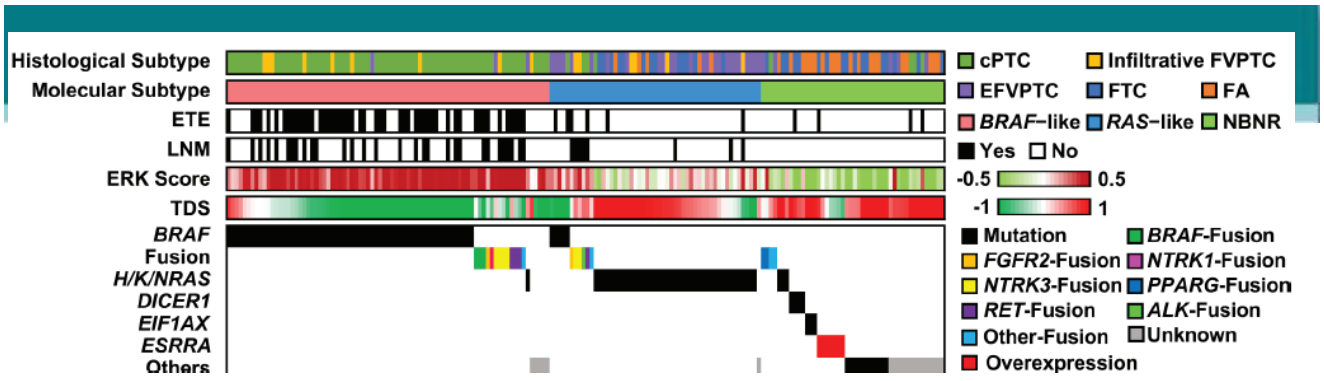
Bethesda III: 10-15% de malignidade

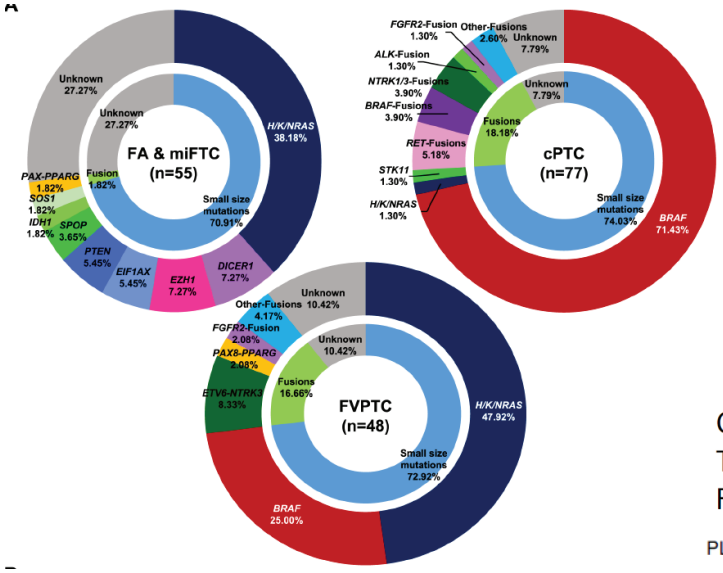
CONDUTA

Tireoidectomia total: Carcinoma papilífero variante folicular em lobo esquerdo, com 1.3cm, com comprometimento de cápsula. Extensão extra-tireoidiana e invasão vascular não detectadas. Margens livres, porém uma é exígua (menor de 1mm). Presença de uma paratireoide na peça

CARCINOMA PAPILÍFERO DE RISCO INTERMEDIÁRIO







Comprehensive Analysis of the Transcriptional and Mutational Landscape of Follicular and Papillary Thyroid Cancers

PLOS Genetics | DOI:10.1371/journal.pgen.1006239 August 5, 2016

TESTES MOLECULARES

-Classificador de expressão gênica (**Afirma**): *"rule out cancer"* - **$3200**

-Painel de mutação de 7 genes: **miRInform (Asuragen),** agora **ThyGenX (Interpace)**: *"rule in cancer"* - **$1675**

-ThyroSeq v2.1 (CBL Path): *"rule in cancer/rule out cancer"*(?) - **$2250**

-ThyGenX+ThyraMIR (Interpace): *"rule in cancer/rule out cancer"*(?) - **$1675+4000**

NECESSÁRIO SABER A PREVALÊNCIA DE CÂNCER INSTITUCIONAL EM BETHESDA III, IV e V

	VPN *("rule out test")*	VPP *("rule in test")*
Asuragen	86%	**88%**
Afirma	**95%**	40%
ThyroSeq 2.1	97%	**80%**
ThyGen X + ThyraMIR mir-THYpe	94% **95.9%**	**75%** 76.1%

TESTES MOLECULARES

Quando indicar **"rule in test"**?

#Prevalência institucional de câncer é alta nos nódulos suspeitos à PAAF;
#Critérios ultrassonográficos de alto riso (nódulos arredondados, margens irregulares, infiltrativos, microlobulados, microcalcificações, calcificação em casca com componente de extrusão para partes moles, evidência de EET) com hipoecogenecidade – **70-90% de malignidade;**
#Bethesdas III,IV preferencialmente;
#Busca de mutação específica (BRAF);
#Cirurgiões que tem como rotina TT independente do tamanho (não seguem ATA)

Em que contribui um **"rule in test"**?

#Ajuda a definir a extensão da tireoidectomia;
#Diminui em 2.5 vezes o risco de complementação de tireoidectomia;
#Ajuda principalmente quando BRAF mutado: apresenta alto VPP;

Não contribui...

#RAS ou PAX8/PPAR-gama mutado: cai o VPP. Muitos são NIFTP, adenomas. Indicação não mudará e seguirá o que PAAF já ditou: lobectomia diagnóstica ou tireoidectomia parcial em função do tamanho

CASO CLÍNICO 2

#EAGU, **sexo feminino, 53 anos**, com nodulações tireoidianas descobertas ao realizar ultrassom cervical de rotina.

#TSH: 4,46mIU/mL, T4livre: 0,87ng/dl

#**Ultrassom da tireóide**: tireoide com formações nodulares ligeiramente heterogêneas, bem definidas e regulares, ovaladas, isoecogênicas, uma polar inferior à direita (1,3cm), duas no polo superior à esquerda (0,6 e 1,3cm), todas categoria 3 ao US. **Presença de nódulo na metade inferior à esquerda (3,9cm), esta com macrocalcificações fragmentadas e microcalcificações agrupadas no interior, categoria 4 ao US.** Todas as lesões apresentam componente hipervascular periférico e central à avaliação Doppler fluxométrica colorida. Cisto de paredes finas e regulares com 7mm, com imagem puntiforme hiperrefringente mural, no terço médio do lobo direito, avascular. Ausência de linfonodomegalias cervicais.

CASO CLÍNICO 2

#PAAF de nódulo do lobo esquerdo da tireoide de 39mm: suspeito para neoplasia folicular – Bethesda IV

PAAF de nódulo de lobo esquerdo da tireoide de 12mm: Bethesda I

PAAF de nódulo de lobo direito da tireoide de 10mm: Bethesda III

#CONDUTA?

- **Tireoidectomia parcial esquerda diagnóstica?**
- **-Tireoidectomia total?**
- **Repuncionar nódulos?**
- **Teste molecular?**
- **Observação clínica?**

PACIENTE SEM DESEJO DE OPERAR!!!

CASO CLÍNICO 2

MIR-THYPE®
CLASSIFICADOR MOLECULAR DE TIREOIDE POR MICRORNA

#Realizado perfil de expressão de microRNA do nódulo do polo inferior do lobo esquerdo com mir-THYpe: **BENIGNO**

#Optado por seguimento clínico com novo ultrassom em 6 meses

VALOR PREDITIVO NEGATIVO (VPN)

Significa que a probabilidade de um resultado "BENIGNO" estar errado é de apenas 4%

TABLE 6. SONOGRAPHIC PATTERNS, ESTIMATED RISK OF MALIGNANCY, AND FINE-NEEDLE ASPIRATION GUIDANCE FOR THYROID NODULES

Sonographic pattern	*US features*	*Estimated risk of malignancy, %*	*FNA size cutoff (largest dimension)*
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule ***with*** one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE	>70–90[a]	Recommend FNA at ≥1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins ***without*** microcalcifications, ETE, or taller than wide shape	10–20	Recommend FNA at ≥1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, ***without*** microcalcification, irregular margin or ETE, or taller than wide shape.	5–10	Recommend FNA at ≥1.5 cm
Very low suspicion	Spongiform or partially cystic nodules ***without*** any of the sonographic features described in low, intermediate, or high suspicion patterns	<3	Consider FNA at ≥2 cm Observation without FNA is also a reasonable option
Benign	Purely cystic nodules (no solid component)	<1	No biopsy[b]

HAUGEN ET AL.
THYROID
Volume 26, Number 1, 2016

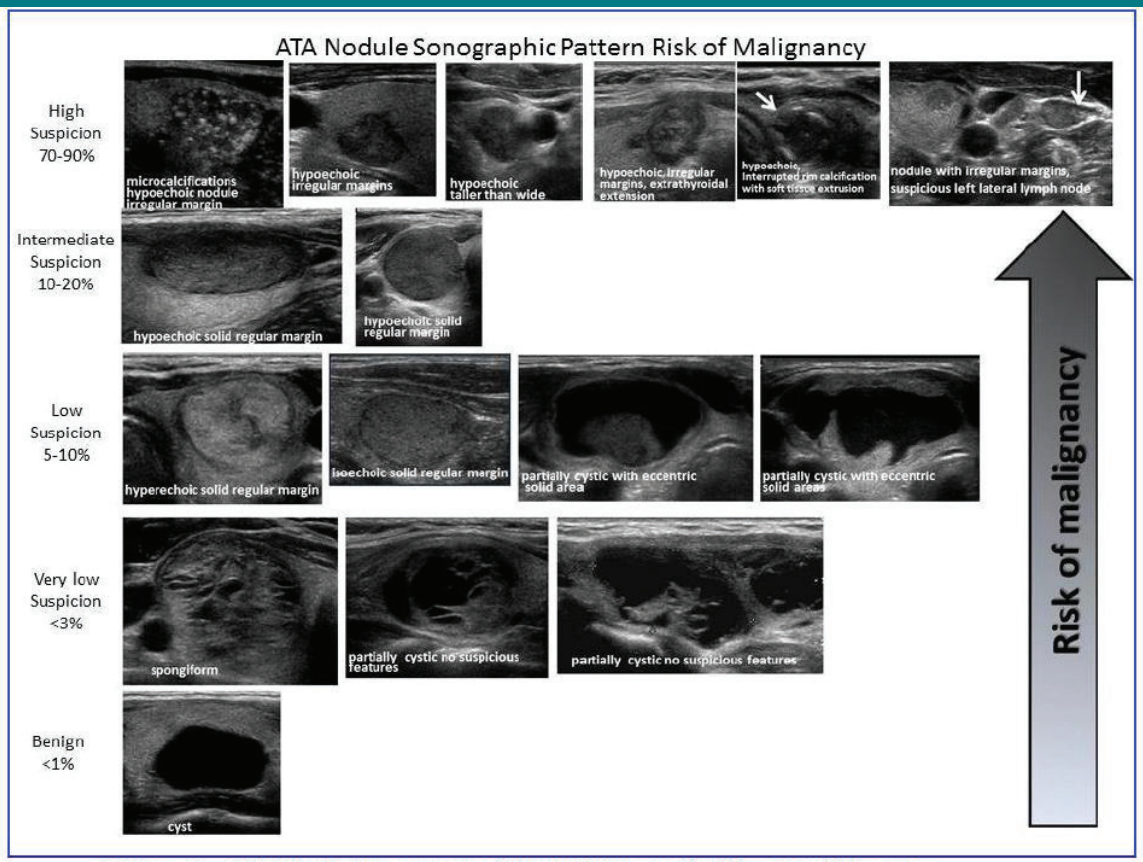


Figure 2. ATA nodule sonographic patterns and risk of malignancy

CASO CLÍNICO 3

#MVCP, 21 anos, sexo masculino, foi submetido em setembro de 2013 à tireoidectomia total com excisão de cisto tireoglosso e linfadenectomia recurrencial bilateral. Patologia mostrou carcinoma papilífero variante folicular da lesão no hioide, com 7,5cm de diâmetro, comprometendo a margem cirúrgica, com infiltração de tecido gorduroso e muscular adjacente, além do osso hioide. Presença de invasão angiolinfática, lobos tireoidianos normais, 5 linfonodos recurrenciais livres de neoplasia.

#Junho 2014: **tireoglobulina=1.378**, TSH=54, anti-Tg=16 ao receber 100mCI. PCI mostra presença de metástases funcionantes em pulmões e mediastino (estádio II).

#Julho de 2014: **tireoglobulina=236**, TSH=15,96

#Janeiro de 2015: nova dose de I131, 100mCI. PCI mostrou metástases funcionantes de carcinoma diferenciado em pulmões. **Tireoglobulina=1456**

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CASO CLÍNICO 3

#Setembro de 2015: tireoglobulina=51,48, TSH=0,002. TAC tórax mostra múltiplas metástases pulmonares. Relutante em realizar I131.

Em dezembro/2015 recebeu 250mCI, com **tireoglobulina=450**, TSH=312. PCI mostra metástases pulmonares concentrantes de I131.

#Outubro de 2016: **tireoglobulina=239,32** e TSH=286. Recebeu 150mCI. PCI mostra captação difusa em pulmões.

#**DOSE ACUMULADA DE I131= 600mCI**

#Agosto de 2017: recebeu 100mCI. **Tireoglobulina= 138,44**, TSH=453. PCI mostra metástases pulmonares captantes. Prescrito PuranT4 275mcg.

#Março de 2018: recebeu 100mCI. **Tireoglobuina=127,66**, TSH=510. PCI mostra metástases iodocaptantes em pulmões e região cervical direita. Ultrassom cervical SED. TAC tórax mostra estabilidade dos múltiplos nódulos pulmonares bilaterais exceto por alguns no pulmão direito com aumento dimensional: apical do LSD (5mm para 8mm) e do lobo médio (9mm para 1,3cm).

DOSE TOTAL ACUMULADA DE 800mCI

#Conduta:
1- Manter doses de I131?
2-Realizar PET-CT?
3- Terapia-alvo?

The efficacy of RAI therapy is related to the mean radiation dose delivered to neoplastic foci and also to the radiosensitivity of tumor tissue (922). The radiosensitivity is higher in patients who are younger, with small metastases from well-differentiated papillary or follicular carcinoma and with uptake of RAI but no or low ^{18}FDG uptake.

(A) Pulmonary micrometastases should be treated with RAI therapy and RAI therapy should be repeated every 6–12 months as long as disease continues to concentrate RAI and respond clinically because the highest rates of complete remission are reported in these subgroups.

Radioiodine-avid macronodular metastases may be treated with RAI and treatment may be repeated when objective benefit is demonstrated (decrease in the size of the lesions, decreasing Tg), but complete remission is not common and survival remains poor. The selection of RAI activity to

Letter of apologize

Dear Readers,

We would like to apologize for not having published the jornal of the last year (2018) The Hospital Universitário Evangélico and Faculdade Evangélica do Paraná were both under judicial intervention and auctioned at the end of November 2018. The entire staff of both institution had a hard time without funds for scientific production.

Now we are in a phase of hope with new direction of the Instituto Presbiteriano Mackenzie This is 180 year Instituition dedicated to teaching and researches.

We are sad to say goodbye to our old hospital that did so much for de unfortunate patient! But we are also glad to continue our work with a direction of the Instituto Mackenzie.

We are like FENIX: we are reborn from the ashes!

Editors of the Revista de Endocrinologia & Diabetes Clinica e Experimental

Instructions for the publication of the Journal Endocrinology & Diabetes Clinical and Experimental

The journal follows the International Committee of Medical Journal Editors

01 All the manuscripts will be published in English. The journal accepts original articles, preliminary notes, case reports, review articles, updates and letters to editor. There a topic dedicate to internal medicine linking endocrinology and medical clinic. The journal strongly encourages on line submissions of manuscripts. Those should be accompanied by a title, keywords and an abstract in English for the purposes of international registration. Abstracts in other languages may also be attached.

02 The articles received by the Editor will be analyzed with the Assistance of the Editorial Board. Minor changes to "copy desk" can be effective with the purpose of standardizing the articles, without substantial changes in original text.

03 Manuscripts can be sent on CD or via on line to publicacao@revistaendocrino.com. The text should be typed on pages containing 20 to 24 rows and rows with 70 to 75 spaces, with the objective of enabling the diagramming the calculation of space required for each article. The word processor used must be either Microsoft Windows compatible program (Word, Write etc.).

05 The article must have title, full name of the authors; quote from site (full address) where out performed the work; full titles of authors, key words (or "keywords") without exceeding a limit of 250 words; introduction; material or material and methods or description of the case; results; discussion and/or comments (when applicable); conclusions (when applicable); summary (summary in English), consisting in the correct version of the summary, not exceeding 250 words; references (as quoted below in item 08) in alphabetical order; the accompanying illustrations must follow appropriate rules, described in item 07.

06 Illustrations are of figures and graphs referred to in Arabic numerals (example: fig. 3, graph 7), in the form of ink drawings photographs ECG EEG etc. When possible must be submitted in original form. The illustrations will be accepted only allow good reproduction. Should not be glued in the middle of the article text and it must be attached with the respective legends typed on the bottom of the same (one sheet for each illustration). Must take care to number each illustration on the back of the same and indicate the correct place where should be introduced. Tables and frames are specified in Arabic numerals, consisting always the respective title, accurately. Tables and frames without its description in the text and are intended to summarize the article. The units used to express the results (m, g, g/100 ml, etc.) will appear at the top of each column. It will be up to the Editor to judge excessive illustrations (figures, tables, graphs, tables etc.), deleting the redundant.

07 The references must follow the alphabetical order or the order of appearance in the text. Showing them all authors cited in the text. It must be contain: name of author, name of the journal abbreviated in accordance with the criteria used in the Index Medicus (www.nlm.nih.gov/tsd/serials/lji.html). Papers accepted but not yet published may be included in the references. You should avoid using as reference poster or free themes from conferences unless they are of high relevance. Articles published online may be cited in the references and should bear the name of the site as well as the date of access.Chapter of Book: Ruch, TC.Somatic Sensation. In Ruch T C et al. Neurophysiology. Philadelphia Saunders 1963; 330-332 Journal article: R.W.G Gruessner, Sutherland D.E.R, Najarian j. S, et al. Solitary pancreas transplantation for non uremic patients with insulin-dependent diabetes mellitus labile. Transplantation 1997; 64: 1572-77.

08 The names of drugs cited in the text (names of fantasy, officers, patented, and acronyms of chemical research) shall comply with corresponding regulations of the World Health Organization, according to rules summarised by KOROLKOVAS, a.-Regulatory Editorial Nomenclature-Names of drugs (Drug Nomen--clature). Rev. Bras. Clin. Terap. 5: 1976 (February).

09 The authors will receive ten copies of the issue in which their work was published (for reprints), which will be sent directly to the place where the work performed. Reprints must be ordered and previously combined with the Commercial Direction.

10 The manuscripts that don't fit the standards or that does not suit the needs of the journal editorials may be forwarded to the authors to carry out the necessary adjustments that will be indicated in the personal letter from the Editor. Will be mentioned the dates of receipt and approval of work for publication, in order to safeguard the interests of the author's priority. In the case of re-routing of work to adapt to our rules for publication, the date cited is always receive the first forwarding of work. The content of the articles is the responsibility of the authors. The link between the author (s) and pharmaceutical laboratories, as well as another source that is generating resources must always be quoted by author (s). The copyright of the manuscripts are of the magazine in question.

11 Will be given top priority in the publication of articles and/or notes that they concerned about matters directly or indirectly related to the basic purpose of the journal Endocrinology & Diabetes Clinical and Experimental

12 Studies that involve animals, research or human, should obey the rules of the Helsinki Declaration of 1979 and revised in 2000. The authors is entitled to explanation, if your search is not in accordance with the rules of the Declaration of Helsinki. In addition, when the study involves humans must be approved by the Ethics Committee of your institution.

13 Mailing address of the main author must appear at the end of the article. Your article is your own responsibility, and the same answer for your account both within the medical ethics as in legal proceedings.

14 Structural definition of the main types of articles: Original articles: Articles Are produced through scientific research, presenting original data scientific findings with respect to experimental or observational aspects of Medical Biochemistry and social feature. Includes descriptive analysis and data inferences or own. In its structure should contain the following items: Introduction, Material and methods, results obtained and studied by an appropriate statistical method discussion and conclusion. Review articles: Are articles that seek to summarize, analyze, evaluate or synthesize research already published in scientific journals. The revisions are expected to be commissioned by the editors, except in case of scientific relevance for the medical class. Articles from Update or disclosure: These report updated information of interest to the magazine or a new technique or laboratory research. This topic is distinct in its account of the review article. Case report: Present descriptive data about a pathology with academic relevance in relation to the disease, treatment, laboratory or association with another pathology

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