Treatment Induced Neuropathy of Diabetes

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Background

1. Gibbons CH, Freeman R. Treatment-induced diabetic neuropathy: a reversible painful autonomic neuropathy. Annals of neurology 2010;67:534-541.
2. Gibbons CH, Freeman R. Treatment-induced neuropathy of diabetes: an acute, iatrogenic complication of diabetes. Brain 2015;138:43-52.
3. Gibbons CH. Treatment Induced Neuropathy of Diabetes: An Autonomic Dysrecognition Syndrome. Clinical Autonomic Research 2016;26:1.
4. Gibbons CH. Treatment induced neuropathy of diabetes-Long term implications in type 1 diabetes. J Diabetes Complications 2017.
5. Gibbons CH, Goebel-Fabbri A. Microvascular Complications Associated With Rapid Improvements in Glycemic Control in Diabetes. Current diabetes reports 2017;17:48.
6. Gibbons CH. Treatment-Induced Neuropathy of Diabetes. Current diabetes reports 2017;17:127.
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8. Kihara M, Zollman PJ, Smithson IL, Lagerlund TD, Low PA. Hypoxic effect of exogenous insulin on normal and diabetic peripheral nerve. AmJPhysiol 1994;266:E980-E985.
9. Tesfaye S, Malik R, Harris N, et al. Arterio-venous shunting and proliferating new vessels in acute painful neuropathy of rapid glycaemic control (insulin neuritis). Diabetologia 1996;39:329-335.
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12. Gade GN, Hofeldt FD, Treece GL. Diabetic neuropathic cachexia. Beneficial response to combination therapy with amitriptyline and fluphenazine. JAMA 1980;243:1160-1161.
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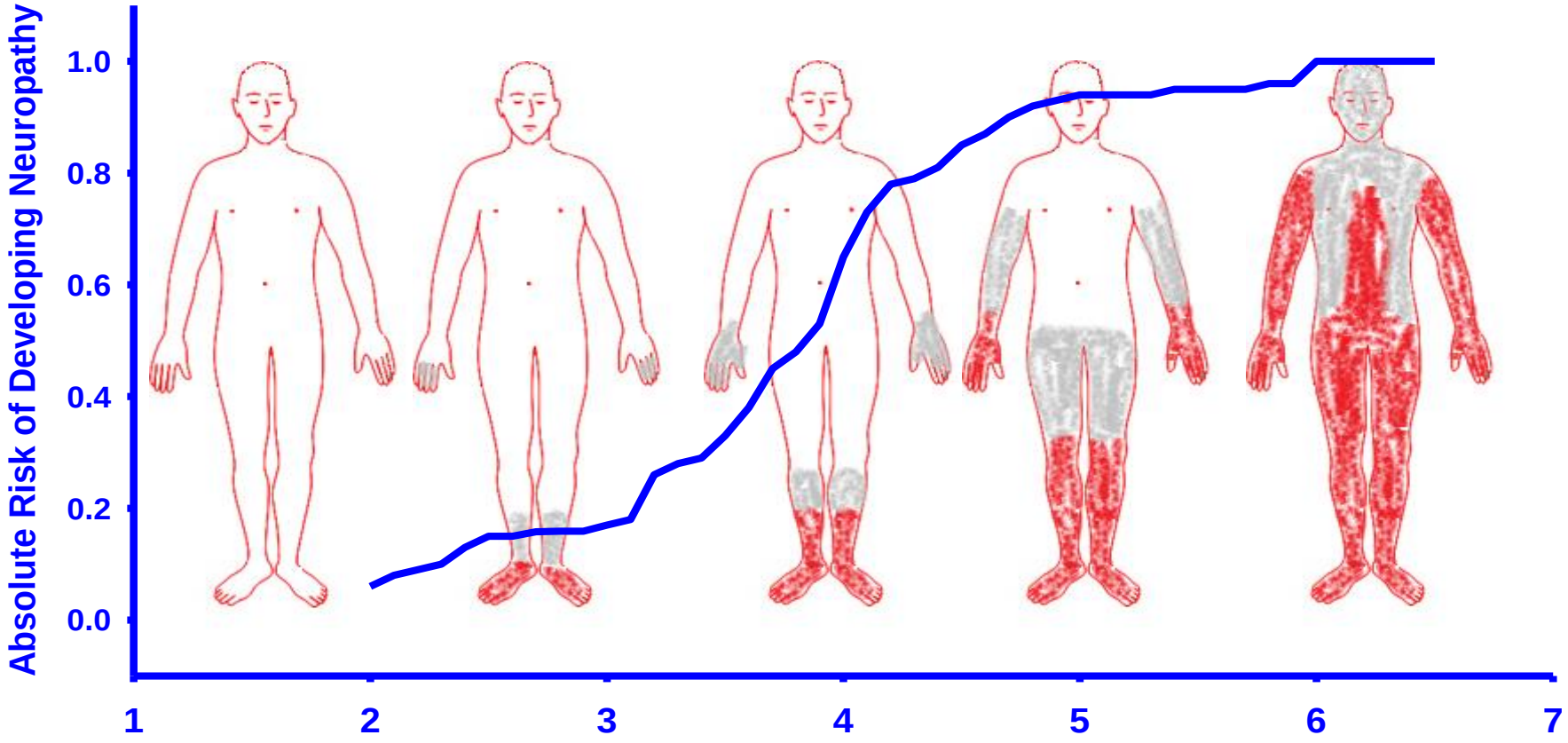
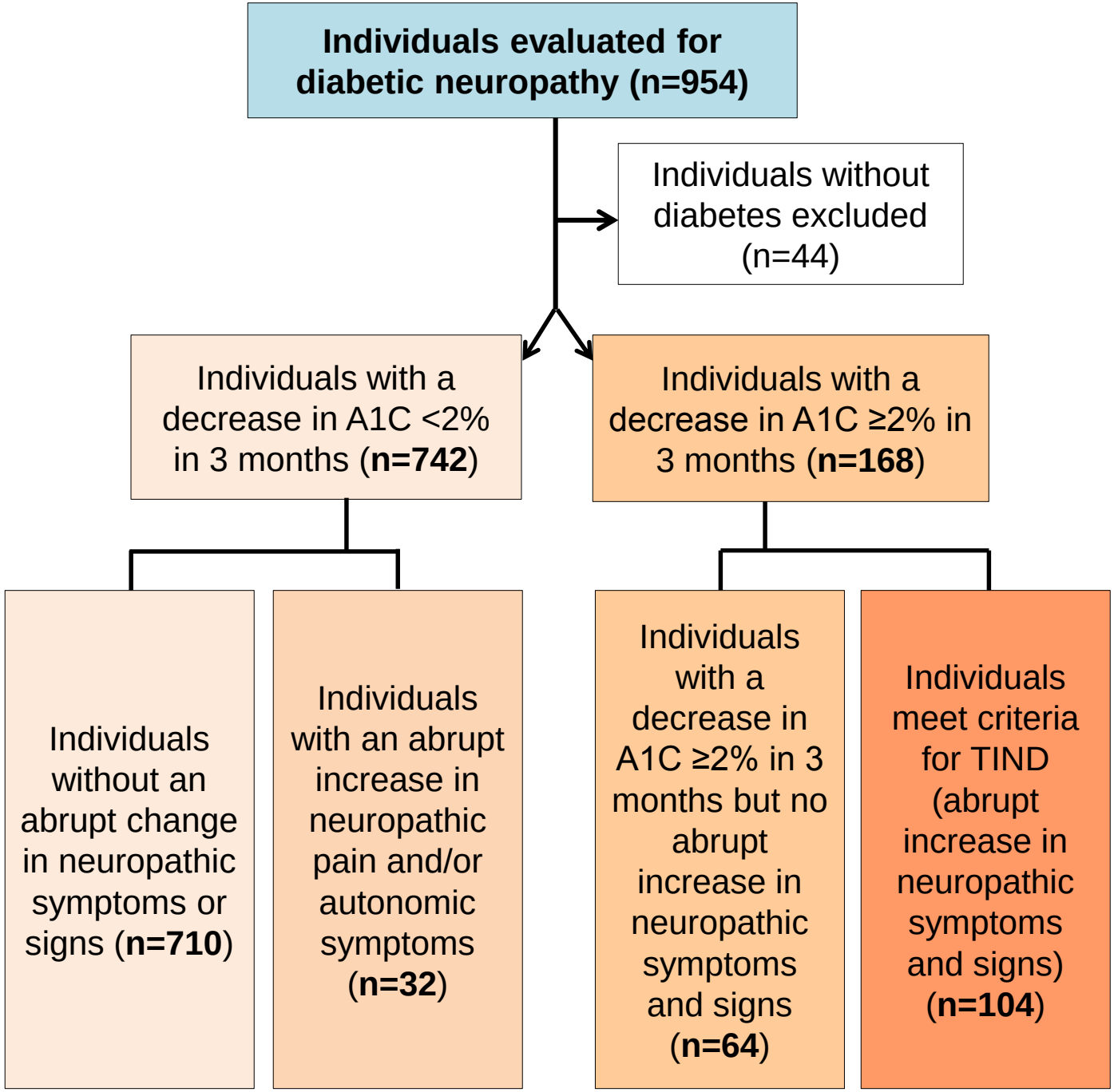
14. Blau RH. Diabetic neuropathic cachexia. Report of a woman with this syndrome and review of the literature. ArchInternMed 1983;143:2011-2012.
15. Jackson CE, Barohn RJ. Diabetic neuropathic cachexia: report of a recurrent case. JNeurolNeurosurgPsychiatry 1998;64:785-787.
16. Grewal J, Bril V, Lewis G, Perkins BA. Objective evidence for the reversibility of nerve injury in diabetic neuropathic cachexia. Diabetes Care 2006;29:473-474.

DISTRIBUTION OF NEUROPATHIC PAIN

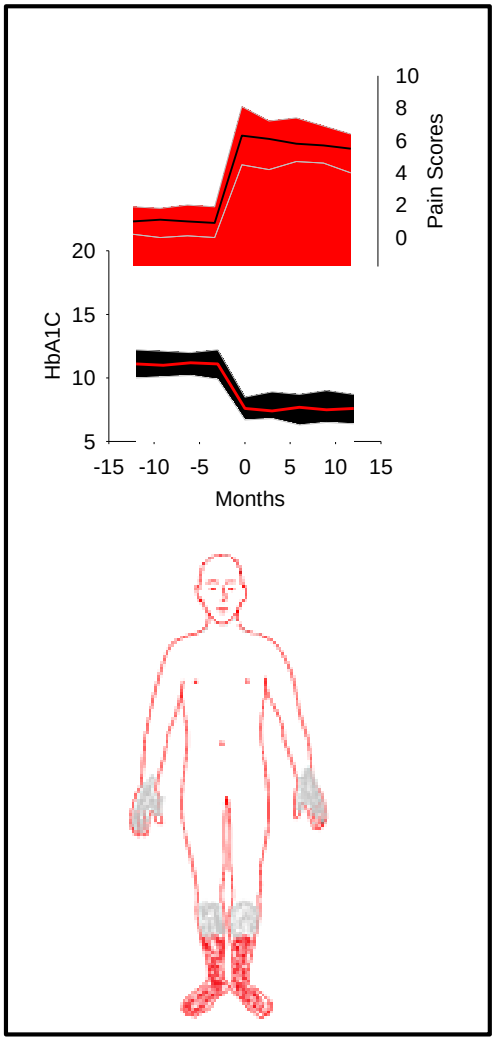


SEVERITY OF NEUROPATHIC PAIN

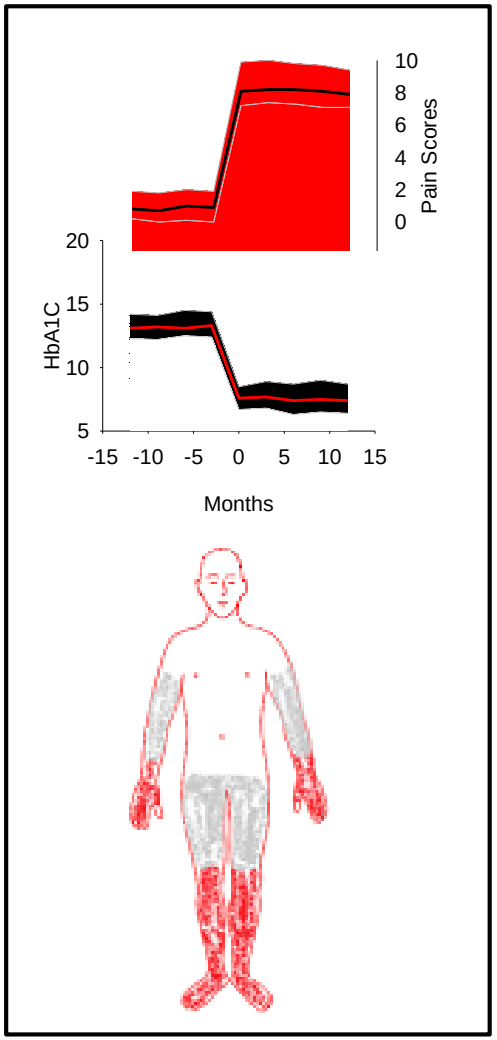

Individuals evaluated for diabetic neuropathy (n=954)
Individuals without diabetes excluded (n=44)
Individuals with a decrease in A1C <2% in 3 months (n=742)
Individuals with a decrease in A1C ≥2% in 3 months (n=168)
Individuals without an abrupt change in neuropathic symptoms or signs (n=710)
Individuals with an abrupt increase in neuropathic pain and/or autonomic symptoms (n=32)
Individuals with a decrease in A1C ≥2% in 3 months but no abrupt increase in neuropathic symptoms and signs (n=64)
Individuals meet criteria for TIND (abrupt increase in neuropathic symptoms and signs) (n=104)

TIND: Neuropathic Pain

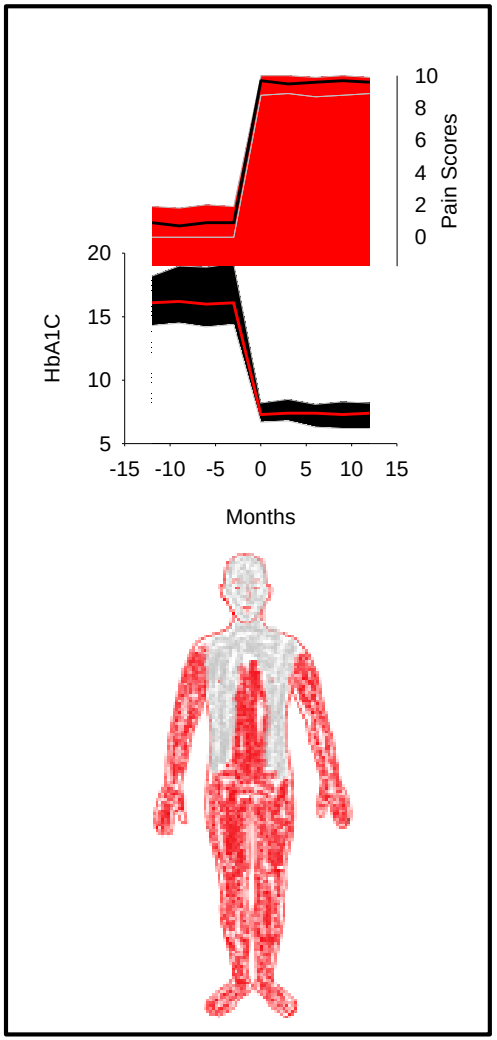
A1C Decrease 2-3.9%



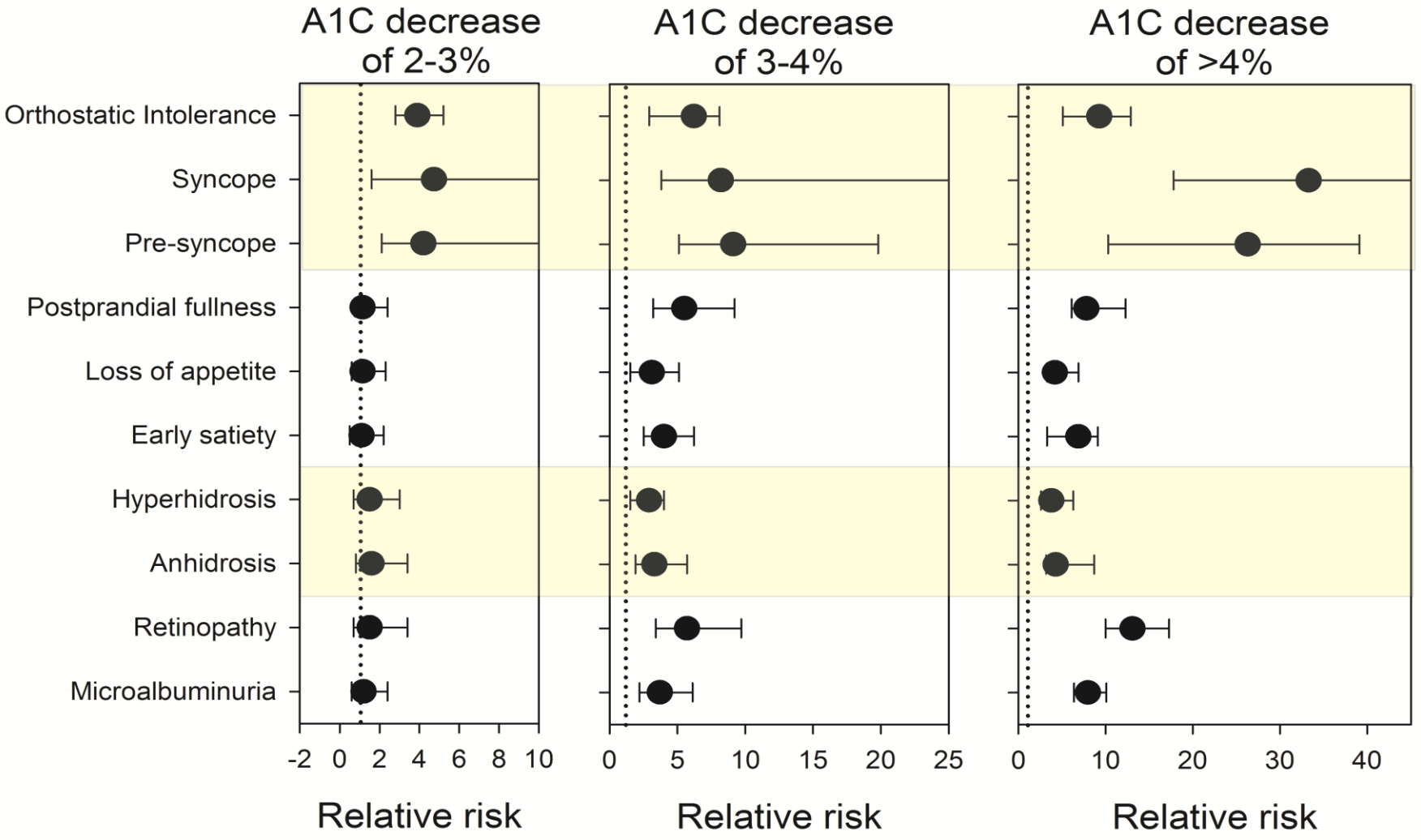
A1C Decrease 4-7%



A1C Decrease >7%



TIND


A1C decrease of 2-3%
A1C decrease of 3-4%
A1C decrease of >4%
Orthostatic Intolerance
Syncope
Pre-syncope
Postprandial fullness
Loss of appetite
Early satiety
Hyperhidrosis
Anhidrosis
Retinopathy
Microalbuminuria
-2 0 2 4 6 8 10
0 5 10 15 20 25
0 10 20 30 40
Relative risk
Relative risk
Relative risk

Core Diagnostic Criteria

Diagnostic Criteria	Potential Controversy/Limitation
Small fiber sensory or autonomic neuropathy	Some rare cases of motor involvement now seen in recurrent episodes of TIND
Decrease in HbA1C of ≥2 points over 3 months	Is there a better solution than just HbA1C (i.e is 11-8 = 15-12), or would glucose meter records be better?
Pain increase by >3 points on an 11 point Likert scale and/or autonomic dysfunction developing over a period of 2 weeks of sufficient severity to cause patients to seek medical attention	Does this time frame needed to expanded or contracted
Pain and/or autonomic dysfunction occurs within 8 weeks of glycemic change	Does this time frame need to be expanded or contracted?

Proposed Diagnostic Criteria

Diagnostic Criteria
An acute small fiber sensory or autonomic neuropathy that can progress to involve myelinated sensory or motor fibers
Decrease in HbA1C of ≥2 points over 3 months or equivalent decrease in daily blood glucose monitoring levels in the setting of at least 6 months of sustained hyperglycemia*
Pain increases by >3 points on an 11 point Likert scale and/or autonomic dysfunction develops over a period of 2 weeks of sufficient severity to cause patients to seek medical attention
Pain and/or autonomic dysfunction occurs within 8 weeks of glycemic change
Other forms of diabetic neuropathy do not prevent the development of TIND

Limitations and areas of research needed

- Much of the existing research is from a single center and therefore high risk of referral bias
- Duration of hyperglycemia required to cause TIND is not well established
- Relative change in glucose levels vs. change in HbA1C – it is the absolute amount of change or the proportion of change that matters?

Differential Diagnosis

- Diabetic lumbosacral radiculoplexus neuropathy*
- Length dependent diabetic small fiber neuropathy
- Drug/toxin induced neuropathies
- Inflammatory or infectious neuropathies

1. Core Diagnostic Criteria Table

Criteria

1. The acute onset of a small fiber sensory or autonomic neuropathy by neurologic examination, neurophysiologic testing or neuropathologic testing.
    1. Neurological examination may not fit existing scales. Expanded UENS as a potential option?
2. Symptoms and signs occurs within 8 weeks of an improvement in glycemic control:
    1. A decrease in HbA1C of ≥2 points over 3 months or
    2. A decrease in daily blood glucose monitoring levels equivalent to an HbA1C change of ≥2 points
3. Pain increases by >3 points on an 11 point Likert scale and/or autonomic dysfunction develops over a period of 2 weeks of sufficient severity to cause patients to seek medical attention
4. Pain is length dependent (although may appear as whole body pain in some cases)
5. History of sustained hyperglycemia of at least 6 months
6. There is no other diagnosis that better explains the neuropathy

2. Common Features: Demographics

- Type 1 diabetes more common, more frequent in women
  - Occurs with insulin
- Type 2 diabetes less common, male:female ratio equal
  - Occurs with insulin, oral hypoglycemic medications, strict diet initiation

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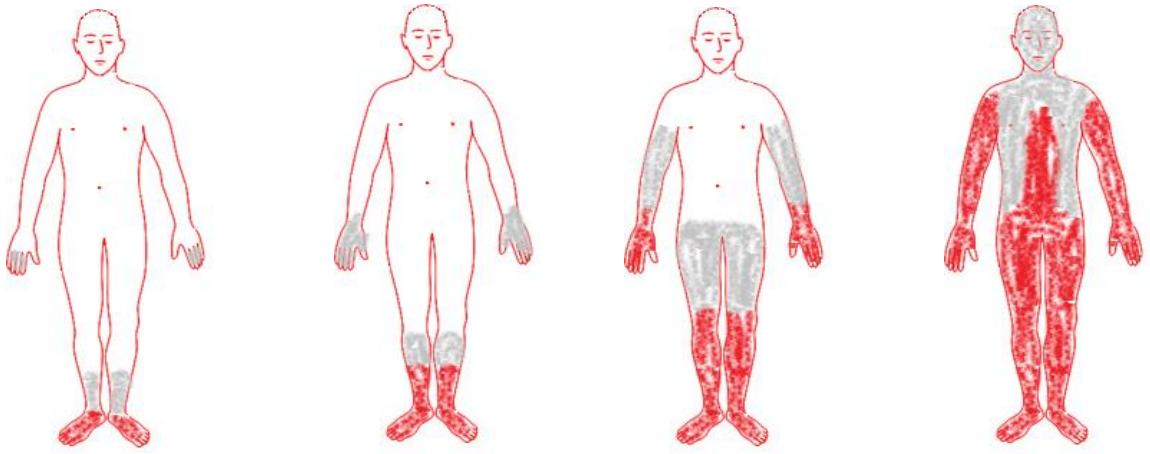
2. Common Features: Pain

- Small fiber neuropathic pain – ‘hot, burning, stabbing, lancinating’ pain
  - Pain is often the presenting symptom
  - Severity of pain linked to magnitude of change in HbA1C



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2. Common Features: Other Complications

- Autonomic symptoms are common, but often unreported because of focus on pain
  - Autonomic testing frequently shows widespread autonomic involvement, may be subclinical
- Associated with renal and retinal involvement (early worsening retinopathy well described in the literature)
  - Severity linked to magnitude of glycemic change

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2. Common Features: Epidemiology

- Limited data available
- In a single center study 11% of patients referred for evaluation of diabetic neuropathy had TIND

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2. Common Features: Lifespan Considerations

- In type 1 diabetes, can occur in the pediatric population
  - Possibly in type 2 diabetes as well with population trends in obesity, but not reported to date...
- In more severe cases, significant risk of morbidity and mortality (data limited at this time)
- Vision loss, renal failure and amputations all reported

Gibbons CH. Treatment induced neuropathy of diabetes-Long term implications in type 1 diabetes. J Diabetes Complications 2017

3. Common Medial and Psychiatric Comorbidities (Type 1 DM)

- Eating disorder history extremely common
  - More common in women with T1DM than women without DM
  - Diabulemia, intentionally withholding insulin to lose weight
  - Predisposition to rapid changes in glucose control

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Gibbons CH, Goebel-Fabbri A. Microvascular Complications Associated with Rapid Improvements in Glycemic Control in Diabetes. Curr Diab Rep 2017

Goebel-Fabbri AE. Disturbed eating behaviors and eating disorders in type 1 diabetes: clinical significance and treatment recommendations. Current diabetes reports 2009.

Custal N, Arcelus J, Aguera Z, et al. Treatment outcome of patients with comorbid type 1 diabetes and eating disorders. BMC psychiatry 2014.

Colton PA, Olmsted MP, Daneman D, et al. Eating Disorders in Girls and Women With Type 1 Diabetes: A Longitudinal Study of Prevalence, Onset, Remission, and Recurrence. Diabetes Care 2015.

Dickens YL, Haynos AF, Nunnemaker S, Platka-Bird L, Dolores J. Multidisciplinary residential treatment of type 1 diabetes mellitus and co-occurring eating disorders. Eating disorders 2015.

de Groot M, Golden SH, Wagner J. Psychological conditions in adults with diabetes. The American psychologist 2016.

3. Common Medial and Psychiatric Comorbidities (Type 2 DM)

- Hypertension
- Hyperlipidemia
- Tobacco use
- History of ‘medical denial’

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Gibbons CH, Freeman R. Treatment-induced neuropathy of diabetes: an acute, iatrogenic complication of diabetes. Brain 2015.

4. **Neurobiological**, psychosocial, risk factors, protective factors

- Unknown mechanisms of disease at this time
- The rapid length dependent development of neuropathy could suggest an energy failure
  - Mitochondrial dysfunction
  - Axonal transport failure
- Inflammatory mediators – hypoglycemia causes cytokine release and hyperalgesia

Low PA, Singer W. Treatment-induced neuropathy of diabetes: an energy crisis? Brain 2015;138:2-3.

Dotson S, Freeman R, Failing HJ, Adler GK. Hypoglycemia increases serum interleukin-6 levels in healthy men and women. Diabetes Care 2008;31:1222-1223.

Razavi NL, Kitabchi AE, Stentz FB, et al. Proinflammatory cytokines in response to insulin-induced hypoglycemic stress in healthy subjects. Metabolism 2009;58:443-448.

Gibbons CH, Adler GK, Bonyhay I, Freeman R. Experimental hypoglycemia is a human model of stress-induced hyperalgesia. Pain 2012;153:2204-2209.

4. Neurobiological, **psychosocial, risk factors**, protective factors

- Significant psychosocial risk factors: eating disorders risks, 'medical denial' risks
  - Both leading to prolonged hyperglycemia
  - Frequent psychologic event that triggers change in glycemic control
- Potential opportunities for high risk target identification (eating disorders in type 1 DM, or newly diagnosed type 2 diabetes)
- Multifactorial interventions to prevent TIND recurrence will require study

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4. Neurobiological, psychosocial, risk factors, **protective factors**

- Protective factors – unknown
- Theoretical approaches – mitochondrial health
- Slower glycemic change
- Anti-inflammatory interventions, blunting of cytokine release

5. Functional Consequences

- Diffuse microvascular involvement
- Severe pain – typically requiring significant polypharmacy
- Autonomic dysfunction – Syncope, gastroparesis, erectile dysfunction
- Renal failure
- Retinopathy
- Amputations
- In some cases – progression to large fiber neuropathy with motor weakness

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Conclusions

- Limitations:
  - Limited prospective data
  - No validated questionnaires selectively studied for validity in these cases
  - NIS-LL and UENS have been studied
  - UENS has a more dynamic range for this problem but won't capture any potential motor involvement

Diagnostic Criteria
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Conclusions:

- Key aspects of future research agenda
  1. Strategies to identify those at risk prior to development
  2. Does altering the rate of glycemic change alter the disease?
  3. Are there preventative therapies that can be introduced prior to glycemic change?
     1. Energy use (mitochondrial)
     2. Anti-inflammatory, cytokine release
  4. Are there salvage therapies that can be considered after TIND development?