新陳代謝科

醫護工作手冊

台中榮民總醫院內科部新陳代謝科

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民國一百年二月 修訂

民國一百零三年七月 修訂

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第一章: 糖尿病人住院時的評估

(一)詢問病史：

1.瞭解病史可以幫助我們對糖尿病診斷的確立。

2.若已有糖尿病的病人，則要瞭解過去和現在治療的情形，血糖控制的程度，和評估有無糖尿的慢性併發症。

3.詳細的病史可以提供給我們治療的計劃和繼續照護的基礎。

4.詳細的病史應該包括：

(1)與糖尿病診斷有關的實驗數據。

(2)過去糖化血色素的記錄。

(3)飲食習慣，營養情況，體重，小孩時和青少年時的生長與發育狀況。

(4)過去的治療計畫，包括營養和自我照護教育。

(5)糖尿病的治療史，如藥物，飲食計劃，和血糖的監測記錄。

(6)運動治療計劃史。

(7)酮酸中毒或低血糖的發生次數。

(8)感染病史，如皮膚，腳，牙齒，和生殖泌尿道等的感染。

(9)有無服用會影響血糖的藥物。

(10)動脈粥狀硬化的危險因子，包括：抽菸、高血壓、肥胖、高血脂和家族史。

(11)糖尿病和其他內分泌疾病的家族史。

(12)懷孕史，有無妊娠糖尿病史，或出生嬰兒大於4000公克者。

(13)生活型態、文化背景、教育程度、經濟狀況等，都會影響糖尿病的治療。

(二)理學檢查

1. 糖尿病人易引起併發症的器官，包括：眼睛、腎臟、腳、神 經、心臟，和血管。

2. 若血糖控制不好的病人，則易發生感染。

3. 糖尿病的小孩，若血糖控制不好，則會影響生長與發育。

4. 要注意有無引起繼發性糖尿病的病史或病徵，如胰臟炎、hemochromatosis、acromegaly、pheochromocytoma 和 Cushing's syndrome 等。

此外理學檢查尚應包括：

(1)測量身高，體重，若是兒童或青少年，則要與正常者比較。

(2)性成熟狀況。

(3)量血壓，包括躺和站立時的血壓。

(4)眼底檢查。

(5)口腔檢查。

(6)甲狀腺觸診。

(7)心臟和腹部的檢查。

(8)脈搏的評估。

(9)手和腳的檢查。

(10)皮膚的檢查，包括胰島素注射部位的檢查。

(11)神經學檢查，應包括肌力，肌腱反射，溫度，位置，針刺及震動檢查。詳述如下：

a.肌力(Muscle power)：

肌肉之力量(Muscle strength)—癱瘓(Paralysis)意即肌肉之功能完全喪失，而輕癱(Paresis)為肌肉較軟弱無力。肌肉之力量，主觀地可分為六級：(0-5)

5 正常肌肉力量

4 運動可能正常，但其肌肉力量比檢查者之力量小（約減低25％）。

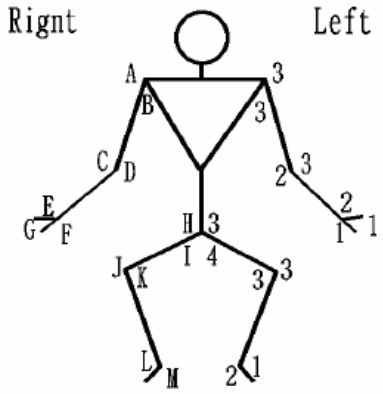
3 可行反地心引力之動作，但稍加外力，即失去支持能力（約減低50％）

2 不能對抗地心引力，例如病人在床上，手腳只能作水平運動（約減低75％）

1 只看到肌肉收縮，但無關之運動。

0 完全不能運動，即沒有肌肉收縮。

檢查結果，用下面之簡圖表示，如C代表肘關節屈曲的力量，即肱二 肌，肱肌及肱橈肌等的共同的力量。D代表肘關伸張的力量，即肱三頭肌的力量。



b.肌腱反射 (Tendon reflexes)：

肌腱反射(Tendon reflexes)—其強弱，主觀地分為五級：

-：作不出來，甚至加強肌腱張力(Re-inforcement)時也沒有反應。

+ ：有反應，但比一般慢而小。

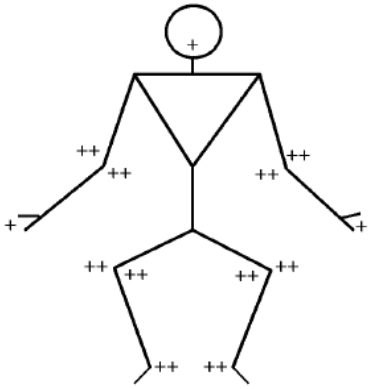
++ ：一般正常的反應。

+++：較增強，可能有毛病，但不一定是病態。

++++：非常靈敏，常併有陣攣(Clonus)。

※肌腱反射的強弱的正常範圍很廣，一方面要兩側互相比較，另外要仔細觀察是否有感覺或運動的缺失、肌肉萎縮、Babinski氏反射等。

將肌腱反射的強度用下面之簡圖來表示：



c.溫度辨別(Temperature discrimination)：

測法如圖所示，一試管中裝冷水，另一試管中裝熱水。兩管的溫差較小時，結果較好，如兩管溫差過小時再換新。試管外要保持乾燥。冷熱試管交換刺激皮膚的時間，要足以引起反應為度。由正常的地區開始測，作為標準，再測有毛病的區域，令病人報告感覺。左右比較，並劃出大略的病變區來。

d.位置感覺(Position sense)：

測法如圖所示，把腳趾和手指如圖搬上搬下，先讓病人看看測者的搬動方向。然後要病人閉眼說出腳趾或手指移動的上下方向。

e.針刺(Pin-prick)：

大頭針的尖銳刺激(Sharp stimulation)和手指的鈍刺激(dull stimulation)均可測試。先測試病人手腳感覺正常的區域，慢慢往感覺異常的區域測試。針頭刺激和手指刺激的交換過程，同時詢問病人到底是尖銳刺激或鈍刺激。若病人回答遲疑或異常感覺時，便可能有神經病變，而劃出病變的範圍。

f.震動(Vibration)：

檢查用音叉，頻率是每秒256，檢查時敲打音叉，然後把音叉置於腳大趾上，和手指背面的骨頭上，和interal 和lateral malleolus上（如圖所示）。要病人說出有無震動，令病人報告震動何時停止。

※ 自律神經系統檢查

自律神經系統檢查，其實可針對身體好幾個系統分別加以評估。如：心血管系統、消化系統、泌尿生殖系統或表面流汗功能等。但這其中以心血管系統、自律功能檢查的敏感度最好，也較具特異性。此外檢查方法也較不複雜，在病房邊即可實施。

1. 躺站心速率改變反應：

病人先安靜躺著數分鐘之後，貼上心電圖電極片於四肢，並觀察第二導程（Lead II）之心電圖波。這時請病人做起來（或站立），然後計算坐起來或站起來後第15次前後心跳的RR間隔及第30次前後心跳RR間隔，並求其比值。一般而言，坐起來以後，第15次心跳前後的心速率最快，而到第30跳前後時，會有一反射性的心速減慢。

2. 深呼吸心速率改變反應：

請病患採安靜坐姿，然後以吸氣5秒、吐氣5秒的速度調整病人的呼吸速率（每分鐘共6次呼與吸cycle）。待呼吸穩定之後，如前於四肢貼上心電圖電極片，並觀察Lead II。然後計算一分鐘內，最快的心跳數與最慢心跳數，並將其相減，求得差異值。依此法，再求得另外2次的呼吸cycle，並計算最快與最慢的心跳數差異。最後以3次的差異值做平均。

3. 躺站血壓改變反應：

病患安靜躺於床上，並測量血壓（含收縮壓、舒張壓），這時請病人站起來（或坐起來）至少一分鐘後，再測量同一手臂的血壓。最後計算收縮壓與舒張壓的差異值。

4. 第30跳RR間隔：第15跳RR間隔：□ 1.04正常，1.01-1.03 borderline，□1異常；深呼最心速~最慢心速：□ 15次/ 分正常，11-14次/分borderline，□10次/ 分異常，血壓改變反應。

收縮壓下降值□10 mmHg正常，11-29 mmHg borderline，□ 30 mmHg異常，舒張壓下降值□10 mmHg正常，11-20 mmHg borderline，□ 20 mmHg異常，

(三)實驗室檢查

1.空腹血漿葡萄糖。

2.糖化血色素（HbA_1C）。

3.空腹血脂肪：總膽固醇，HDL-C、TG、LDL-C。

4.血清Creatinine，收集二十四小時尿液，每日蛋白流失量和白蛋白和Ccr。

5.尿液常規:葡萄糖,尿酮,總蛋白或白蛋白,同時比較單次尿中creatinine與albumin之尿中比值。

6.若有泌尿道感染的症狀，要作尿液培養。

7.心電圖。

四、治療計劃

1.短期和長期的治療目標。

2.藥物治療，如胰島素，口服降血糖藥，抗高血壓藥，降血脂藥，Aspirin，及其他藥物。

3.營養治療，會診營養師。

4.生活型態的改變，如運動，戒煙，減重。

5.自我照護和自我管理教育。

6.血糖自我監視，尿液酮體的測定。

7.會診眼科醫生，作眼底的檢查與治療。

8.足部照護。

9.如有必要，可照會各種專業人員，包括醫師、護理人員、營養師、心理衛生專家、運動專家、和藥師等。

10.教導病人，有無法解決的問題時，或有急性併發症時，如何與醫師或其他醫療團隊成員聯絡。

11.持續性的支持與追蹤。

12.口腔衛生。

13.懷孕前及懷孕時，加強血糖控制。

※ 糖尿病酮酸及高血糖高滲透血症住院時的評估

On critical (depends on clinical conditions)

NPO

On CVP line (as necessary if impaired renal、heart functions)

I/O monitoring

ON NG tube、Foley catheter (if patient in comatous state)

Blood culture、urine routine/culture、CXR、KUB if fever

Monitoring:

At the first 12 hours ：
Check the blood sugar q1-2 hours
Serum、Na、ABG q6h、check the I/O q8h、CVP q6h and vital signs q4h
At the next 12 hours ：
Check the BS q4h、Na、 K q12h、ABG q12h
檢驗次數應視病人實際情形做調整，HHNK，DKA usually should be subsided in 18-24 hours
病人如有其他underlying problems such as infection、MI、CVA等應視各別狀況處理

第二章 甲狀腺與頸部淋巴腺檢查

甲狀腺與頸部淋巴理學檢查乃完整身體檢查不可或缺的一環，但往往因臨床醫師的疏忽或不熟悉此一部分的檢查，而喪失掉早期幫病患診斷甲狀腺疾病的先機。如Graves' disease，只要病人臨床上有甲狀腺機能亢進的症狀，再加上觸診發現瀰漫性甲狀腺腫，聽診有bruit，此時病人縱然還沒有甲狀腺功能報告，你大概也有七八成的把握說病人為Graves' disease。另外如病人出現sore throat, headache, fever等症狀，在外面已逛過很多OPD，但仍查不出所以然。這時只要仔細檢查病人的甲狀腺，若發現其硬而腫大，subacute thyroidits的診斷自可油然而生，病患的困擾也可迎刃而解。又如thyroid nodule，其理學檢查特性為had, fixed, tenderness，又可摸到頸部淋巴結，雖然尚未實施細胞學檢查，大概也要高度懷疑是否為惡性腫瘤。這些例子大概都告訴我們甲狀腺與頸部淋巴理學檢查的重要性。以下篇幅將分別以視診、聽診、扣診與觸診方式，配合圖片介紹甲狀腺與頸部淋巴腺的檢查。

1. 甲狀腺解剖位置

頸部乃連接頭部與身體軀幹之構造，在此一區域內包含有肌肉、頸動脈、頸靜脈、淋巴結、神經、氣管、食道、及頸椎等組織器官，它們皆為頭部與軀幹間的重要交通工具。此外頸部尚包括有兩種內分泌腺

體—甲狀腺和副甲狀腺，它們分別對身體能量與鈣離子代謝扮演重要角色。甲狀腺乃人體內最大的內分泌腺體，在成年人的一般重量約為10至20公克。甲狀腺之解剖結構可分為左右兩葉，中間部分由峽部連接。一般而言，峽部恰位於環狀軟骨之下，剛好在甲狀腺軟骨尖部（喉結）與胸骨上切跡的中間，並橫跨第二、第三與第四的氣管軟骨環。至於左右二葉其平均長度約為2.5-4公分寬度1.5-2公分，厚度1-1.5公分。二葉皆大概橫跨於甲狀腺軟骨與第六的氣管軟骨環間。

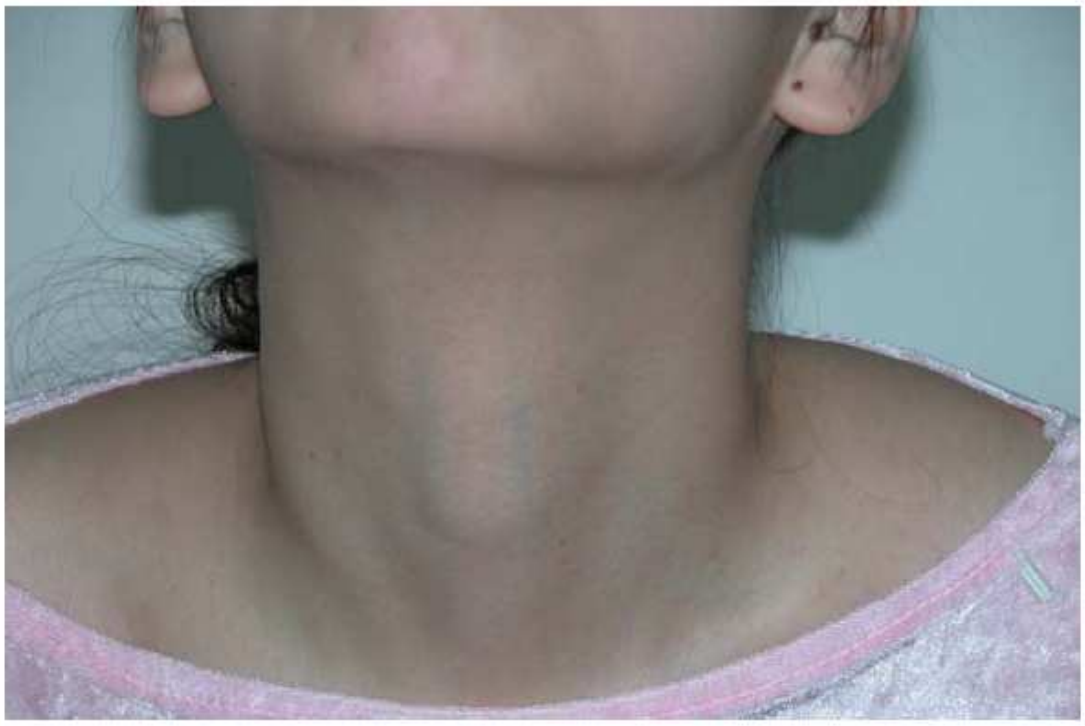
2. 甲狀腺視診

在進行甲狀腺視診時，需注意到四要點：

- 檢查者的位置站在病人頸部前方，病患採坐姿。
- 適度的光源來自檢查者適度的光源來自檢查者的後方，光線進行方向恰能切過頸部表面
- 病人頸部姿勢需略保持伸張狀態(頭部後仰，下巴往上翹)
- 準備一杯水，必要時請病人將水含於口中，以利吞嚥動作。

首先請辨認甲狀腺軟骨、環狀軟骨、氣管、胸鎖乳突肌及胸骨上切跡等結構，並請記住甲狀腺解剖位置（如前述）。一般而

言，正常大小之甲狀腺於視診時並無法看到。但是於一些脖子較為細長之人，視診時可能看到甲狀腺。視診時需注意整個甲狀腺左右兩葉的對稱性、表面是否有任何腫塊、甲狀腺是否隨著吞嚥有上下起伏，以及甲狀腺下緣是否明顯可見，這些都是在作甲狀腺視診時需注意的。此外於視診時，亦可觀察氣管是否有偏離一側，以及有無其他的不正常腫塊。



3. 甲狀腺聽診

聽診一般於甲狀腺理學檢查，不常被用到。但是如於觸診後發現甲狀腺有腫大情形，而且臨床上疑有機能亢進，這時可利用聽診器橫膈面做聽診檢查。請將聽診器置於甲狀腺左或

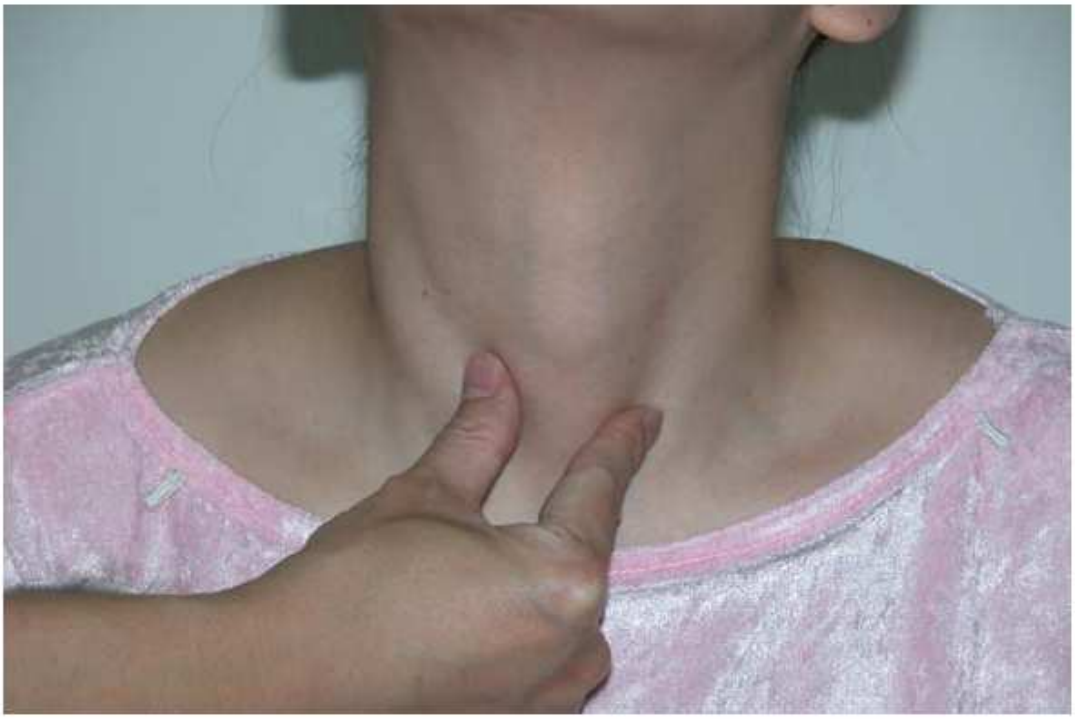
右葉，如病患為Graves' disease，可能聽到心收縮期或心收縮期與舒張期之連續雜音。此一雜音出現，表示甲狀腺處於高血流狀態。

4.甲狀腺觸診

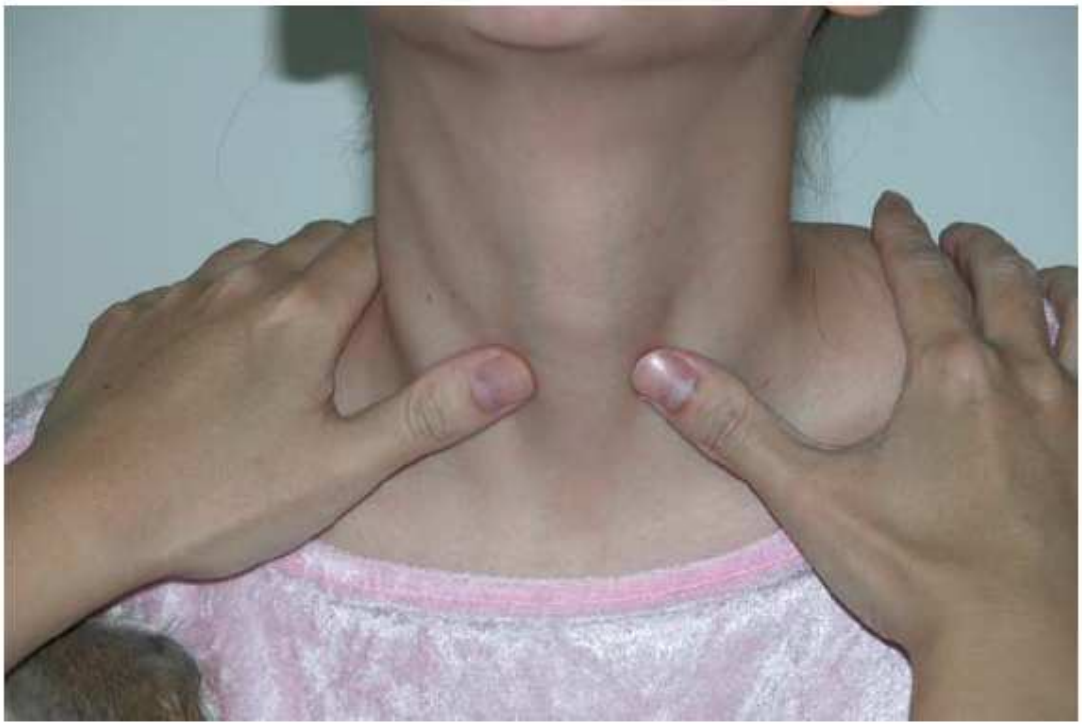
觸診乃甲狀腺理學檢查中最重要的。觸診時，檢查者的位置可站於病患的前面或後面，至於選擇何方式，可依各人習慣決定。正常大小的甲狀腺於觸診時大部分都摸不到。以下介紹３種不同的觸診方法

(I) 檢查者站於病人的右肩前方，面對病患並讓他能看到你。請病人的脖子略為彎曲，臉略朝向左側，這將可鬆弛左邊的胸骨乳突肌。伸出你的右手大拇指先找到環狀軟骨，再沿著氣管向下滑行，並試著感覺甲狀腺的峽部。一般而言，峽部寬度多為幾毫米而已，若是大於

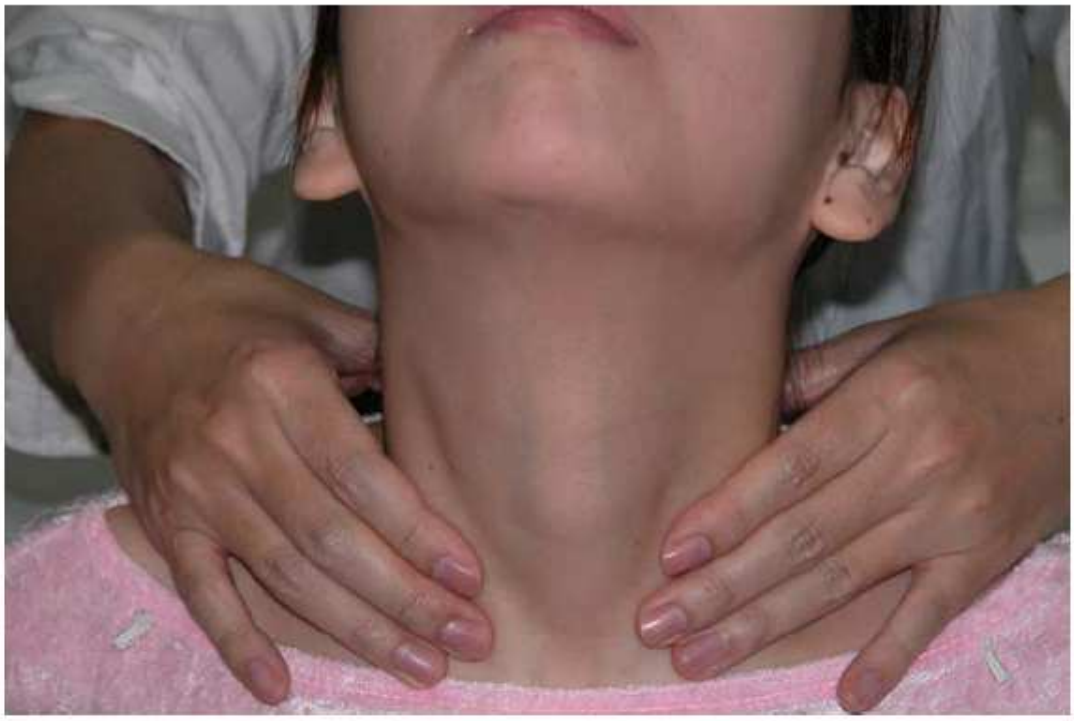
一公分以上，表示可能已有甲狀腺腫。再來利用右手第二、第三指置於氣管與左邊胸骨乳突肌內側緣間接（手指方向約與氣管呈45°），從甲狀線軟骨的高度，沿著氣管與胸骨乳突肌內側緣間往下檢查甲狀腺的左側葉。手指的壓力要溫和，檢查當中可請病人喝水做吞嚥動作。請注意甲狀腺大小、軟硬、有無結節以及有無辦法摸到甲狀腺之下緣等。（右側葉請依上述相反方式進行）



（II）檢查者面對病人的正前方，伸出雙手的大拇指分置於氣管兩側。先檢查環狀軟骨下的甲狀腺峽部。然後再沿著氣管與胸骨乳突肌內側緣間從甲狀腺軟骨的高度，往下檢查甲狀腺的左右葉。請利用右拇指將氣管略為向病患左旋轉，以利左拇指觸摸右葉（左葉方法為相反方式）。手指的壓力要溫和，檢查當中可請病人喝水做吞嚥動作。請注意甲狀腺大小、軟硬、有無結節以及有無辦法摸到甲狀腺之下緣等。



（III）檢查者站於病人的正後方，伸出雙手的第二、三、四手指分置於氣管兩側。亦先檢查環狀軟骨下的甲狀腺峽部。然後再沿著氣管與胸骨乳突肌肉側緣間從甲狀腺軟骨的高度，往下檢查甲狀腺的左右葉。請利用左手第二、三、四手指略將氣管推向病患右側，以利右手指觸摸右葉（左葉方法為相反方式）。手指的壓力要溫和，檢查當中可請病人喝水做吞嚥動作。請注意甲狀腺大小、軟硬、有無結節及是否能摸到甲狀腺下緣等。

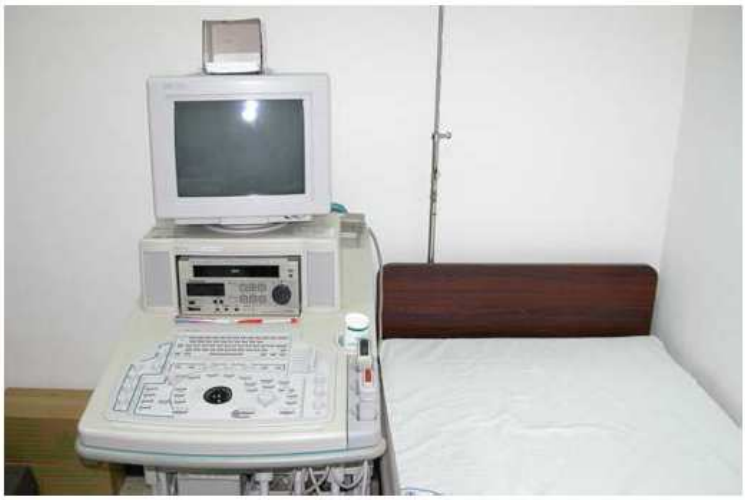


5.甲狀腺之扣診

一般而言，扣診於甲狀腺理學檢查中，並不常被用到。唯一情形，如臨床懷疑有胸骨下甲狀腺腫，可於胸骨兩旁作扣診。如聲音由共鳴音變為鈍音，可懷疑病患可能有胸骨下甲狀腺腫。

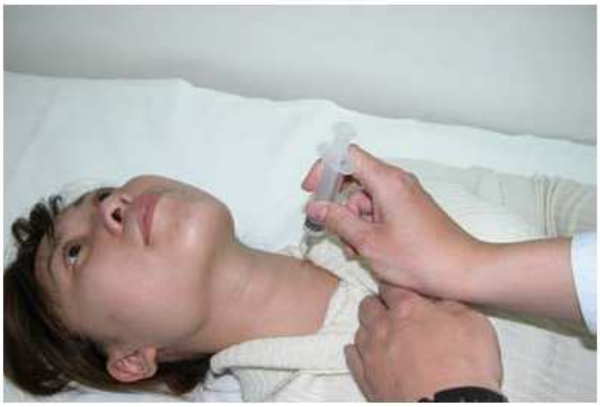
甲狀腺超音波

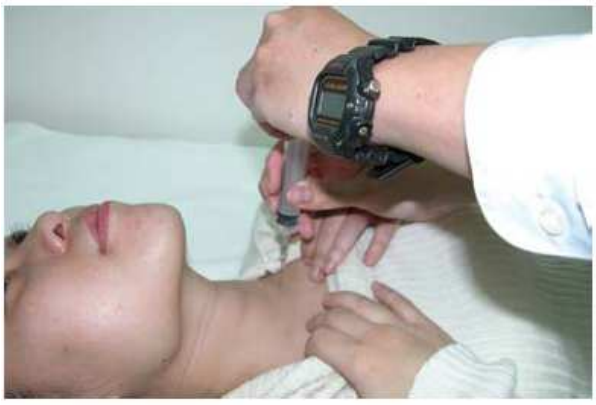
甲狀腺是相當表淺之內分泌腺體，因而在超音波檢查應用上是相當容易，且不需任何準備動作。在檢查時病人是以平躺為宜。然而偶而遇到呼吸衰竭病人或有氣管內管加上呼吸器時，由於在臨床上急於知道甲狀腺腫大之原因，我們也可在半臥情況下施予檢查。由於甲狀腺解剖位置表淺且不大。因而可使用高解像力之探頭，在診斷上則可探測較小之病變。早期之超音波使用5MHz之Grand Scale儀器，解像力較不佳。而目前使用7.5~10MHz Real Time之超音波，對於小於0.5公分之病變，偵測效果仍不錯。我們目前使用HP，以10MHZ Real Time來偵測甲狀腺結節。病人在平躺後以枕頭墊在頸部下方，使前項呈伸展狀態。在簡單說明檢查步驟後，將gel塗在前頸部後，先以橫向方式掃瞄，由病人右方至左方掃瞄整個甲狀腺。再以縱向方式掃瞄。在大致了解所檢查甲狀腺解剖位置後，再對可疑之病變位置進行掃瞄。對於異常之位置，探究其病變之性質，大小及深度。



甲狀腺細針穿刺

請病人躺於床上，並儘量讓頭往後仰以利頸部伸張。首先將要抽取的部位皮膚使用酒精消毒，然後將甲狀腺結節固定於左手的第二指與第三指間。這時請病人做吞嚥，確認甲狀腺結節位置，若結節近鄰血管，應儘可能將血管推開。這時右手拿10cc空針，附22號針頭（若為甲狀腺囊腫可用18號針頭），垂直插入結節，若結節有空心與實心部份，應將針頭儘可能插入實心部以利細胞抽取。依台大張天釣教授發明之穿刺技術，建議於針頭插入後，先將針筒原地迴旋三次然後利用左手輕拉針筒後端三次，造成吸力。最後將針頭拔出，然後將細胞打至玻片上，做細胞抹片之用，這時並囑咐病人用酒精棉球壓住抽取部位，一般約10分鐘即可止血，但抽取過程若是刺到血管，最好延長壓迫時間到15至20分鐘。





踝臂動向壓指標檢查（Ankle Brachial Index）

本試驗主要目的乃檢查病患有無週邊動脈血管疾病。檢查主要步驟，首先將Cuff包於左上臂或右上臂。並以8MHZ之音波探頭，測得前臂動脈（Anterior brachial or cubital artery）最大聲音處，並將探頭固定於radial artery處。此時開始充氣，使壓力超過動脈訊號停止時以上10~15mmHg。然後以每秒3至5mmHg放氣，並以探頭偵測動脈訊號直到恢復為止，並記錄當時之血壓值。將Cuff置左或右踝關節之上，並將探頭擺於posterior tibial artery或pedis dorsalis artery上。依上述測定臂動脈壓之方式，測得踝動脈壓。計算踝動脈壓與臂動脈壓之比值（左臂比左踝，右臂比右踝）正常之踝臂動脈血壓指標應大於0.97，若低於此值，應懷疑有週邊動脈血管疾病之可能。

新陳代謝科常見疾病之處置

第一章糖尿病診斷治療與慢性併發症

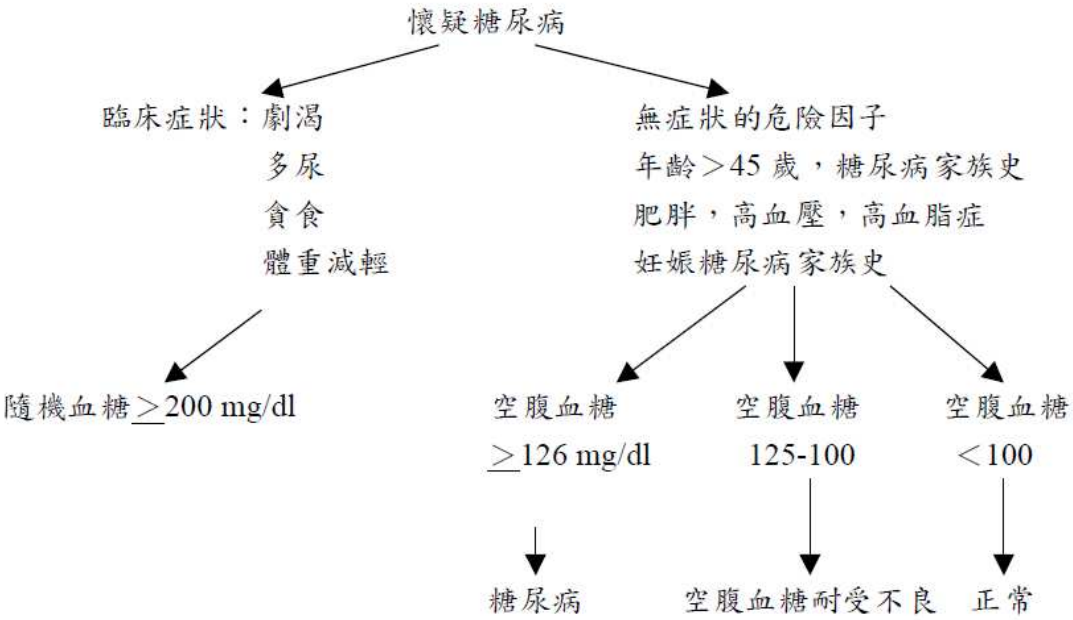
一、無症狀成年人糖尿病和糖尿病前期的篩檢

身體質量指數≧24 kg/m2且具有下列一個以上風險因子者

- 缺乏運動。
- 一等親人罹患糖尿病。
- 高危險的族群（African American，Latino，Native American，Asian American，Pacific Islanders）。
- 生產4 kg 以上嬰兒，或曾診斷為妊娠性糖尿病。
- 高血壓（≧140/90 mmHg）或正接受高血壓治療。
- 高密度脂蛋白膽固醇＜35 mg/dl 和/或三酸甘油酯 ≧250 mg/dl。
- 多發性囊泡卵巢症候群的婦女。
- 曾檢查為葡萄糖失耐或空腹血糖偏高。
- 臨床表現胰島素阻抗（例如：重度肥胖，黑色棘皮症）。
- 曾罹患心血管疾病。

無上述條件的40 歲以上民眾，每3 年篩檢1次，65 歲以上民眾，每年篩檢1 次。

二、糖尿病診斷



三、糖尿病分類

糖尿病在病原學上的分類

I. 第一型糖尿病（β細胞被破壞）

A. 間接的免疫

B. 自發性

II. 第二型糖尿病（顯著的β細胞被破壞到胰島素拮抗）

III. 其它特殊類型

A. β細胞基因缺乏

1. HNF-1α（MODY 3）
2. Glucokinase（MODY 2）
3. HNF-4α（MODY 1）
4. 粒線體DNA
5. 其它

B.胰島素基因功能缺乏

C. 胰臟外分泌疾病

D. 內分泌疾病

1. 肢端肥大症
2. 庫欣氏症候群

3. 親鉻母細胞瘤
4. 腎上腺留鹽激素過多症
5. 甲狀腺機能亢進
6. 其它

E. 藥物或化學因素誘發

1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Diazoxide
5. Dilantin
6. α-interferon

F. 感染

1. 先天麻疹
2. 巨細胞病毒
3. 其它

IV. 妊娠糖尿病

四、糖尿病一般處置

前言

（1） 糖尿病的病症不只是醣類代謝，也包括蛋白質和脂肪，亦非絕對的胰島素分泌機能不全，還有相關不同程度的胰島素拮抗。糖尿病診斷是由血中高血糖或餐後血糖，亦或兩者都有。臨床症狀包括：多尿、劇渴、體重減輕、衰弱和貪食。並非所有的糖尿病都有相同的症狀。

（2） 在糖尿病患中有高達80-90 % 為第二型糖尿病，其餘為第一型或其它類型的糖尿病。

（3） 糖尿病的合併治療：

飲食、運動、口服降血糖藥、胰島素和其它方法。

治療目標：

（1） The DCCT（Diabetes Control and Complicactions Trial, 1993）：長期間的血糖控制以預防或延遲第一型糖尿病的急性併發症。

（2） The United Kingdom Prospective Diabetes Study（UKPDS, 1998）：超過5000位第二型糖尿病患為對象，長達20年的研究發現，良好的血糖及血壓控制可有效降低大血管及小血管病變危險因子。

（3） 美國糖尿病協會建議血糖控制目標（2011）：

生理醫學建議指標 目標

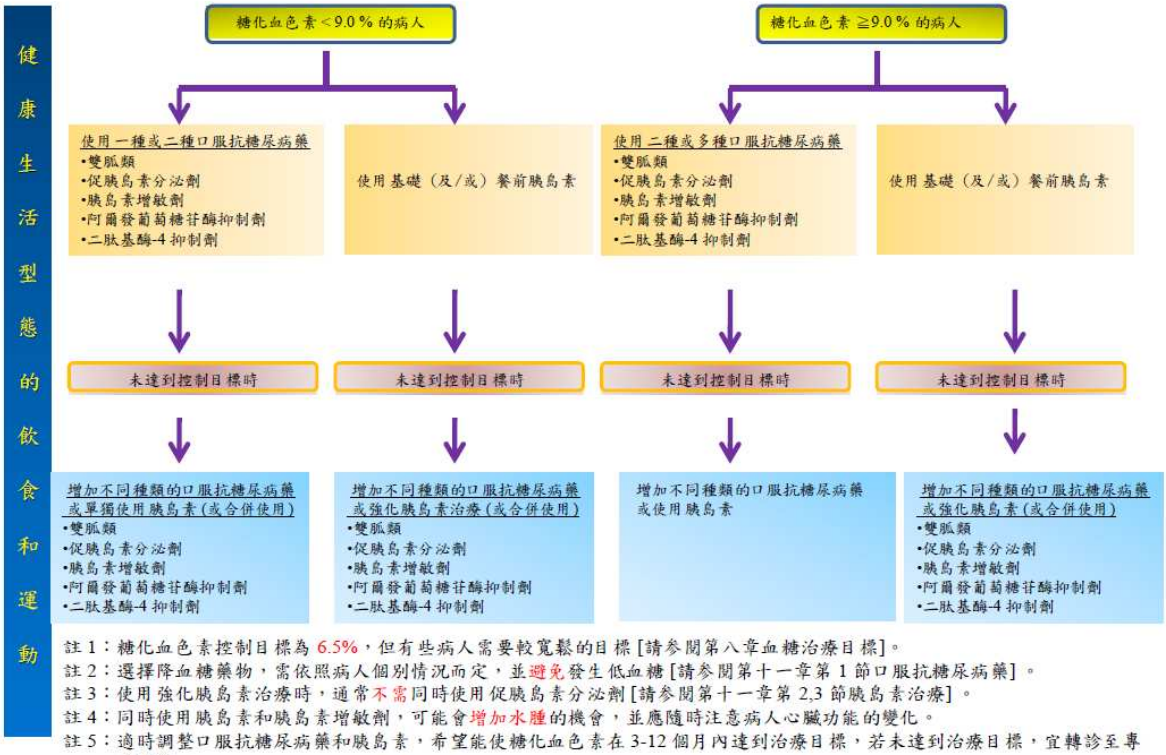
平均空腹血糖 （mg/dl） 70-130

平均飯後血糖 ＜180

糖化血色素（％ ） ＜7

（4） 糖尿病的多種病症：高血脂、血脂異常、高血壓、肥胖等，所有會發展成為心血管疾病的危險因子。

（5） 要預防或延緩發展成心血管疾病（冠狀動脈疾病、腦血管疾病、週邊血管疾病）和其它糖尿病併發症，控制血糖到一定標準與降低罹病率是必要的。



改變飲食和生活習慣

飲食：

（1） 適時減重達到合理範圍。

（2） 每天減少500-1000卡等於每星期減重0.5-1公斤。

（3） 脂質應限制攝取，尤其是三酸甘油酯，亦造成脂肥堆積與肥胖。

（4） 攝取多種醣類，尤其是"低升糖指數"。

（5） 避免飽和脂肪酸及膽固醇。

（6） 食用多元或單元不飽和脂肪酸。

（7） 每天熱量攝取：醣類55-60% 、脂質＜30% 、蛋白質10-20% 。

生活習慣：

（1） 戒煙（非常重要）。

（2） 限制酒精攝取。

（3） 規律的運動（每週至少5次、每次30分鐘）。

口服降血糖藥

Sulphonylureas

前言：

. β細胞表面的接受器和 Sulphonylureas 結合→ 關閉鉀通道（去極化）→ 鈣進入β細胞同時造成胰島素分泌。

. 增加胰島素敏感性：增加葡萄糖運輸（經由葡萄糖轉運子），降低肝釋出葡萄糖（胰臟外效應）。

. 通常血糖控制失敗歸究於未依飲食計劃及運動執行。

. primary failure：使用口服降血糖藥從未達到理想的血糖控制，甚至給予混合劑量亦是。

. secondary failure：每年約有5-10% 因最大劑量未能有效達到血糖控制而失敗。當病人發生自體免疫現象時，便開始緩慢破壞β細胞，此時給藥並非絕對有效的方法。

藥理學：

. 吸收有變異性。

. 大部份會和血中白蛋白緊密結合。

. 經由肝臟代謝轉變為活化形式。

. 經由腎臟排出。

. Glibenclamide：在特定的糖尿病患身上，口服此降血糖藥可能會蓄積在β細胞而增加低血糖的危險性（例如 年紀大、長久糖尿病史、腎功能受損者）。

. 藥物也許會和sulphonylureas作用：

Aspirin、sulphonamides：會與部份血中白蛋白結合，進而增加藥濃度。

副作用：

. 低血糖。

. 體重增加。

. 水份保留和低血鈉症（抑制尿分泌激素平衡效應）

適應症：

. 無法靠飲食和運動控制血糖時。

. 非肥胖病患（在肥胖糖尿病患中，biguanide是more favored agent）。

禁忌：

. 懷孕（也許會穿過胎盤誘發胎兒產生高胰島素血症或低血糖）。

. 併發嚴重病症時（尤其是增加壓力的賀爾蒙，例如epinephrine，也許會造成胰島素分泌及作用受損）。

. 手術期間。

. 年長病患有腎功能受損時（GFR＜100 ml/min）避免長時間作用的藥物。

Meglitinides：

現有 repaglinide 和 nateglinide 二種。主要的作用機轉是與胰臟β細胞上磺醯素受體內的不同部位結合，刺激胰島素的分泌；和磺醯素相較，其吸收速率較快且作用時間較短，因此需隨餐服用。服藥後 10-15 分鐘開始作用，在 1 小時內達到最高濃度，適合用來治療餐後高血糖。Repaglinide 由膽汁排出，而 nateglinide 則由腎臟排出。其與磺醯素相似，非磺醯素的不良反應以體重增加較為常見，但出現低血糖的現象則較磺醯素為少。非磺醯.素不宜與磺醯素合併使用。

Biguanides（Metformin）

前言：

. 延遲，並非減低，小腸中葡萄糖的吸收。

. 在腸壁中，葡萄糖會經醣解異化分解代謝變成乳酸(lactate)，然後再經歷糖質新生作用，在單獨使用biguanides不會發生過低血糖現象。

. 抑制肝中葡萄糖生成。

. 刺激胰島素調節的接受器後作用(post receptor effect)(例如：葡萄糖轉運子）

. 對胰島素分泌無作用。

. 可優先考慮使用在肥胖糖尿病患中。

藥理學：

. 每年約有10% 會失敗。

. 不會導致體重增加。

. 低密度脂蛋白和三酸甘油酯也許會下降。

副作用：

. 乳酸中毒：罕見（給予Metformin每年8/100,000病人）但死亡率較高（＞30% ）

→ 避免給予腎衰竭、呼吸衰竭、心衰竭、肝代償機能減退等病患。

. 腸胃道問題（20-30% ）：胸痛、腹瀉。和食物並用時可減輕約一半症狀。

阿爾發葡萄糖抑制劑（α-glucosidase inhibitors）：

主要作用是在近端小腸抑制澱粉和雙醣類的分解，進而延緩其吸收。此藥不被腸胃道吸收，可降低餐後血糖和胰島素濃度，但降血糖的效果不如磺醯素和 metformin ，單獨使用並不會發生低血糖。使用本藥後，醣類大都在遠側端腸道吸收，因此會產生脹氣和其它腸胃道的副作用。臨床上約有 25-45%的病人因為腸胃道副作用，而停止服用阿爾發葡萄糖..抑制劑 [84,85]。阿爾發葡萄糖..抑制劑可預防葡萄糖失耐的病人發生糖尿病，但其對心血管疾病的預防則有待更進一步的研究。病人服用阿爾發葡萄糖抑制劑如果出現低血糖，治療時必須使用單醣（例如：葡萄糖或牛奶），而不能使用雙醣或多醣，例如：蔗糖（因乳糖.（lactase）不受本藥抑制，但蔗糖.（sucrase）則會受到抑制）。

Thiazolidinedione：

作用機轉為活化 PPAR-γ（peroxisome proliferative-activated receptor-γ），增加肌肉、脂肪和肝臟對內生性或是外源性胰島素的敏感度，降低空腹血糖和血中胰島素濃度。現有 pioglitazone 和 rosiglitazone 二種，常見的副作用有體重增加、體液滯留、周邊水腫和心臟衰竭等。過去的研究顯示，胰島素增敏劑相較於磺醯.素與雙胍類藥物可維持較長期血糖的穩定效果，對糖尿病前期的病人則可降低其疾病進展至第 2 型糖尿病的比例。開始用藥前，應先檢查病人的肝功能（例如：血清轉胺.，ALT），若超過正常上限的 2.5 倍則不建議使用。開始用藥後第 1 年應每 2 個月檢查 1 次肝功能，第 2 年以後視情況檢查。使用中若血清轉胺.超過正常上限的 3 倍，則應考慮停藥。此外，紐約心臟學會（New York Heart Association，NYHA）功能分類第 III 級和第 IV 級心臟衰竭的病人不應使用。胰島素增敏劑可和雙胍類、促胰島素分泌劑和胰島素合併使用。但在某些國家如加拿大，則不建議胰島素和胰島素增敏劑合併使用。

Dipeptidyl peptidase 4 inhibitors，(DPP-4 inhibitors)：

腸促胰液素（incretins）可調節體內葡萄糖代謝，包括類升糖素.-1（glucagon-like peptide-1，GLP-1）和葡萄糖依賴性胰島素刺激多.（glucose-dependent insulinotropic polypeptide，GIP）二種。在生理情況下，GLP-1 和 GIP 會快速的被 DPP-4 水解成不具活性的產物。DPP-4 是位於細胞膜上的蛋白質，能夠在很多的組織中表現，包括免疫細胞。DPP-4 抑制劑是一小分子，和其藉由提高活性腸泌素的濃度，可促進胰島素的釋出和抑制升糖素的分泌，達到降低血糖的作用。Sitagliptin（JANUVIAR）於 2006 年 10 月通過美

國食品藥物管理局核准為第一個口服的 DPP-4 抑制劑，和其它的口服抗糖尿病藥相較，其對體重較無影響。Sitagliptin 會影響免疫功能，因此服用後可能會產生鼻咽炎、上呼吸道感染等副作用。腎功能不全（肌酸酐清除率＜50 ml/min ）時，應減少其劑量。Sitagliptin 可和雙胍類、磺醯.素和胰島素增敏劑合併使用。使用口服抗糖尿病藥、胰島素和二者合併治療

胰島素:

胰島素是人體中調節葡萄糖代謝最重要的荷爾蒙。如果體內胰島素的分泌不足或作用產生障礙時，將會導致血糖上升與糖尿病的發生。第 2 型糖尿病人若合併肝腎功能不良、感染症、高血糖急症或懷孕時，此時必須接受胰島素的治療，以使上升的血糖儘速恢復到控制目標。傳統的胰島素（人類胰島素）依其皮下注射後發揮作用時間的快慢與長短，可分為短效、中效或預混型短中效胰島素。至於結構改變的胰島素類似物，其皮下注射後作用時間則會變的更為迅速（速效胰島素）或更為持久（長效胰島素）或預混型速中效胰島素類似物。胰島素投予路徑除了皮下注射外，也有連續性皮下胰島素輸注的方式。

新診斷的第2型糖尿病，先使用胰島素治療一段時間能增進日後血糖控制。第2型糖尿病人於初診斷時，如其糖化血色素大於9.0%，且同時合併有症狀，例如：體重減輕、全身倦怠等，可考慮先使用胰島素來控制血糖。主要的理由是胰島素將可更迅速矯正病人的高血糖與臨床症狀。此外有一項研究發現，新診斷的第2型糖尿病若先使用胰島素（每日多次皮下注射或幫浦灌注）積極控制血糖2周，之後停止胰島素，並恢復一般傳統式的階梯療法。例如：先使用飲食和運動等生活型態控制，如血糖未達控制目標，則開始予以口服抗糖尿病藥。經過1年後發現，一開始先經過2周胰島素積極控制的第2型糖尿病人，有2倍以上的機率仍不需使用任何降血糖藥物治療，仍能維持血糖於控制目標，而且胰臟β細胞分泌胰島素的能力也較佳。推論其原因可能與使用胰島素治療，而讓胰臟β細胞得到保存休息有關。至於此一益處能維持多久則不清楚，而且能否反應至血糖持續控制良好，甚至減少併發症的發生也不清楚。根據英國前瞻性糖尿病研究顯示，一開始即接受胰島素積極控制血糖的第2型糖尿病人，與先使用口服抗糖尿病藥做積極控制的病人，10年後二組間小血管併發症的發生率並無差異。

第2型糖尿病已使用最大劑量口服抗糖尿病藥，但仍無法達理想血糖控制目標者，若再加上1日注射1次中長效胰島素、1日注射2次預混型胰島素或1日注射3次餐前速效胰島素皮下注射，均能增進糖化血色素與血糖的控制。許多的研究顯示，已使用最大劑量的口服抗糖尿病藥，但血糖控制仍不理想的第2型糖尿病人，如再加上1日注射1次中長效胰島素注射治療，能再降低病人的糖化血色素。例如：選擇接近 24 小時作用的長效胰島素（Glargine或Detemir），或中效胰島素（Neutral Protamine Hagedorn，NPH）。一般而言，使用長效胰島素較不會有低血糖的情形發生。基礎胰島素的起始劑量一般可從 10 U 或從體重kg數的0.1-0.2倍開始。原則上在晚餐後至睡覺前注射1次，每日固定同一時間注射，然後依據

每日自我監測空腹血糖的高低，作為調整胰島素劑量的依據。若血糖未達目標值，可增加注射的劑量，但需注意低血糖的發生與加強低血糖衛教。使用基礎胰島素時，原已使用的口服抗糖尿病藥，通常必須繼續使用，當然也可視血糖的高低或有無其它的副作用，來做為口服抗糖尿病藥刪減的標準。除非有使用上的禁忌，一般建議metformin必須保留。合併使用metformin可以減少體重的增加且較不會發生低血糖。但如果再加上基礎胰島素注射前的血糖不是很高時，則磺醯.素的劑量，可考慮降低或停止。當口服抗糖尿病藥加上1日注射1次的基礎胰島素後，仍無法達到血糖控制目標時，例如：糖化血色素仍高於7.0%，此時可以考慮改為 1 日注射 2 次的預混型胰島素，或改成 3 次餐前注射短效（或速效）胰島素，再加上長效胰島素合併使用。

預混型胰島素的起始注射劑量一般以病人的體重來估算（例如：從未使用過胰島素者，可採用體重 kg 數的 0.4-0.6 倍作為估算總劑量），之後再依據個人的飲食型態與體能活動，將 1 日胰島素的總劑量分配至早、晚餐前。早、晚餐前劑量的增減，則是根據晚餐前和空腹血糖的高低來做調整。至於每日多次注射胰島素劑量的給與，原則上是先計算出1日的總劑量，其中50%的劑量可使用長效胰島素作為基礎胰島素，另50%的劑量則均分為三，作為3餐前速效胰島素的劑量。

在第2型糖尿病人，若以胰島素類似物取代人類胰島素注射，目前並無明顯證據顯示胰島素類似物將更能有效降低糖化血色素，但似乎有較減少低血糖發生的機會和體重增加幅度的趨勢，並較能有效控制餐後高血糖。而使用連續性皮下胰島素輸注是否比每日多次皮下注射胰島素有更好的糖化血色素下降效果，但目前現有的證據並不支持。

各種的胰島素劑型、注射方式及其劑量調整的方法，各有其優缺點，必須視糖尿病人的情況、醫護人員的熟悉度、和病人的接受程度來選擇最恰當的治療方式，才能達到最佳的療效。胰島素治療的過程，病人要定時執行血糖自我監測，而醫師與衛教人員則需定時檢視這些資料，作為胰島素調整的依據。此外也須注意病人是否因積極的血糖控制，而增加其低血糖發生的機會。

各種胰島素製劑

胰島素種類	起始作用時間	最大作用時間	持續作用時間
速效胰島素			
Insulin lispro	5-15 分	30-90 分	3-5 小時
Insulin aspart	5-15 分	30-90 分	3-5 小時
短效胰島素			
Regular insulin	30-60 分	2-3 小時	5-8 小時
中效胰島素			
NPH insulin	2-4 小時	4-10 小時	10-16 小時

各種胰島素製劑

胰島素種類	起始作用時間	最大作用時間	持續作用時間
長效胰島素			
Insulin glargine	2-4 小時	穩定無高峰期	20-24 小時
Insulin detemir	1-3 小時	6-8 小時	18-22 小時
預混型胰島素			
70/30 human insulin	30-60 分	2-8 小時	10-16 小時
70/30 aspart insulin	5-15 分	1-4 小時	10-16 小時
75/25 lispro insulin	5-15 分	0.5-6 小時	10-16 小時
50/50 lispro insulin	5-15 分	0.75-13.5 小時	10-16 小時

五、糖尿病慢性併發症

I. Microvascular complication : include diabetic retinopathy, nephropathy and neuropathy. Those complications are directly related to hyperglycemia and can be prevented by maintaining scrupulous glycemic control.

（i） 糖尿病患與高血壓：

糖尿病患適當的血壓值為130/80 mg/dl，依據JNC-VII標準。然而，假如發現有蛋白尿＞1 gm/day 或有其它器官受損的疾病史（例如：心肌梗塞、中風、腎功能不全），血壓值應降低至120/75 mmHg。

（ii） 腎病變

種類	24 小時收集（mg/24h）	一次收集（μg/min）	點收集（μg/min creatinine）
normal	<30	<20	<30
microalbuminuria	30-300	20-200	30-300
proteinuria	>300	>200	>300

(iii) 糖尿病眼病變：

糖尿病患最常見的眼病變為視網膜病變，包括NPDR及PDR, macular edema etc. 其發生和血糖、血壓、血脂、microalbuminuria皆有關，治療以雷射和手術為主。

(iv) 糖尿病神經病變：

最常見的是 polyneuropathy，可藉由 autonomic function test, MNSI, NCV等方法來診斷。

II. Macrovascular complication : include coronary artery disease, stroke, and peripheral vascular disease. Risk factors for macrovascular disease include insulin resistance, hyperglycemia, microalbuminuria, hypertension, hyperlipidemia, cigarette smoking, and obesity.

III. Miscellaneous complications : such as erectile dysfunction and diabetic foot ulcers.

六、糖尿病急症併發症診斷與治療

(1) 糖尿病酮酸中毒

主要發生在第一型糖尿病，但也會發生在第二型糖尿病。其中約有11% 病患年齡高於60歲，死亡率在有處理經驗的醫院約5%。

診斷：

1. 高血糖（通常血糖高於250 mg/dl）。
2. 低重碳酸鹽（＜15 mEq/L）。
3. 低pH（＜7.3）酮血（>2+）以及增加anion gap。

Table 1—*Diagnostic criteria for DKA and HHS*

	DKA			
	Mild	Moderate	Severe	HHS
Plasma glucose (mg/dl)	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Serum bicarbonate (mEq/l)	15–18	10 to <15	<10	>15
Urine ketones*	Positive	Positive	Positive	Small
Serum ketones*	Positive	Positive	Positive	Small
Effective serum osmolality (mOsm/kg)†	Variable	Variable	Variable	>320
Anion gap‡	>10	>12	>12	Variable
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

*Nitroprusside reaction method; †calculation: 2[measured Na (mEq/l)] + glucose (mg/dl)/18; ‡calculation: $(Na^+) - (Cl^- + HCO_3^-)$ (mEq/l). See text for details.

加速因子：

1. 感染（最常見）（約30-40% ）。
2. 疏忽或未適當使用胰島素。
3. 新診斷的糖尿病患。
4. 情感壓力（大多為青少年）
5. 其它壓力例如手術、創傷、燒傷、敗血症、心肌梗塞、中風等。
6. 未知的原因。

Pathogenesis：

1. 胰島素缺乏：增加脂質解作用(lipolysis)、增加游離脂肪酸。

增加蛋白質分解、肝醣分解。

uninhibited糖質新生作用。

----> hyperglycemia

2. 壓力誘發賀爾蒙調節系統：升醣激素、生長激素、兒茶酚氨、皮質醇。

增加脂質解作用、促進游離脂肪酸釋出。

對抗胰島素作用。

增加糖質新生作用。

3. 增加肝中脂肪酸：增加酮體生成→酮血→酸中毒。

高血糖：滲透性利尿、電解質流失、體積消耗。

治療

I. 評估：

包括酮酸中毒期間液體和電解質的流失：100 ml/Kg、3-5公升或佔成人體重10 % ，鈉流失：7-10 mEq/Kg、Cl：5-7 mEq/Kg。

II. 水分補充治療：

1. 選擇啟始替代液體，應為等滲透壓（最好為生理食鹽水），但如血鈉＞155 mEq/L，可考慮只給half saline。
2. 一開始的1-2小時，給予500-1000cc N/S/hour（在年長病患中應加以修飾）。
3. 接下來的2-4小時，可繼續給予500-1000cc N/S/hour直到vital signs stable or有尿液排出（50-100cc/hr）
4. 4-8小時：0.5N/S 250-500 ml/hr成人、100-250 ml/hr小孩，需包括尿及腸胃道的流失。
5. 當液體流失一半時，可依1. 適當給予16小時（8-24小時）。

III. 胰島素治療：

1. 給予RI（01.-0-15u/Kg），然後持續給0.1u/Kg/hr點滴。

2. 檢查血中葡萄糖q1h約6-8小時、q2h，電解質q2h在剛開始的8小時。
3. 當血糖到達250-300 mg/dl時，液體中可添加葡萄糖（5-10g，葡萄糖，例如：D5W，靜脈注射每小時）。
4. 當血糖到達250且代謝性酸中毒已矯正時，減用RI靜脈注射至 1-2u/hr，直到開始SC胰島素注射。
5. 當酸中毒已矯正及病人可進食時，SC胰島素可以開始使用1/2-2/3u/Kg/day。

IV.鉀的治療：

1. 當血中鉀濃度仍很高時並不建議補充。
2. 當血中鉀濃度3.5-5.5 mEq/dl，開始肌肉注射氯化鉀 20-30 mEq/1000cc fluid。
3. 當血鉀＜3.5 mEq/L，氯化鉀應給予40 mEq/L或更多。

V. 重碳酸鹽的治療：

1. 常規使用仍contraversial。
2. 當血中pH＜7.0或休克、昏迷、敗血症所引起血中pH＜7.1，或乳酸中毒存在時應考慮。

VI. 磷酸鹽治療：

1. 除非血中Ph＜1.0 mg/dl不然不依常規使用。
2. 假如indicated,用30-60 mmol的磷酸鹽，採用注入方式超過24小時。

VII.其它一般照顧：

1. 記錄I/O、維持vital signs、check conscious level regularly。
2. 包括EKG用以判斷是否有心肌梗塞。
3. 使用鼻胃管，預防窒息。

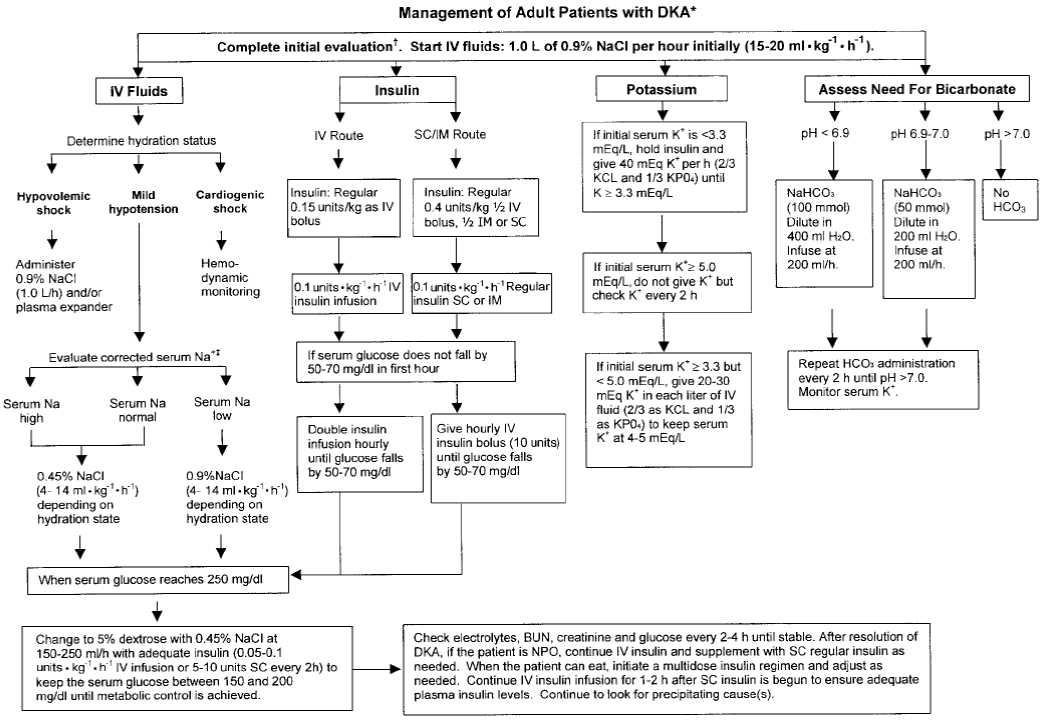


Figure 1—*Protocol for the management of adult patients with DKA. *DKA diagnostic criteria: blood glucose >250 mg/dl, arterial pH <7.3, bicarbonate <15 mEq/l, and moderate ketonuria or ketonemia. Normal ranges vary by lab; check local lab normal ranges for all electrolytes. †After history and physical examination, obtain arterial blood gases, complete blood count with differential, urinalysis, blood glucose, blood urea nitrogen (BUN), electrolytes, chemistry profile, and creatinine levels STAT as well as an electrocardiogram. Obtain chest X-ray and cultures as needed. ‡Serum Na should be corrected for hyperglycemia (for each 100 mg/dl glucose >100 mg/dl, add 1.6 mEq to sodium value for corrected serum sodium value). IM, intramuscular; IV, intravenous; SC subcutaneous.*

酮酸中毒的併發症：

1. 腦水腫

過快降低滲透壓或血糖快速降低。在小孩身上較常見,會有IICP現象。

治療：conservative、甘露醣醇、或肌肉注射decadron以降低腦細胞膨脹，預後差。

預防：勿快速取代鈉、水不足(correct gradual)，initial給予生理食鹽水較好。預防血糖過度快速降低。

2. 急性呼吸困難症候群

負荷過多液體

3. 高血氯酸中毒：

在液體治療期間給過多氯,有不好的臨床效應,應在24-48小時後需要有逐漸修正。

4. 乳酸中毒：

通常在休克或伴隨敗血症現象時存在。可能發生於pH和anion gap無法被胰島素的治療所校正時。

5. 低血鉀：

會引起心律不整。

6. 低血糖

(2) 高血糖高滲透壓非酮性昏迷(Hyperglycemic, hyperosmolar non-ketotic coma)(HHNK)

診斷

1. 血糖大於 600mg/dl

2. 有效滲透壓大於320mOsm/Kg H2O

2 [鈉 + 鉀離子] + 血糖/18

3. 無明顯的酮酸血症，但可能會伴隨嚴重氮血症及乳酸性酸中毒

輕微酸中毒(pH > 7.3) ,重碳酸離子 (HCO3) > 15 Eq/L

死亡率介於15 ~ 58 %

致病機轉

1. 大部分發生在第2型糖尿病病人

2. 壓力 -> 降低胰島素儲備能力 -> 數天內血糖慢慢上升 -> 滲透性利尿作用，低血容量

基礎胰島素分泌不被抑制 -> 不會產生過多的酮體

3.低血容量 -> 由腎臟排泄之葡萄糖受損 -> 腎前氮血症

誘發因子

感染(最常見)，特別是格蘭式陰性菌敗血症；肺炎 (40-60%),泌尿道感染 (5-16%)

降低或停止口服降血糖藥或胰島素

因醫療引起的

含葡萄糖的點滴，全靜脈營養補充，鼻胃管灌食

利尿劑，類固醇，propranolol, phenytoin, diazoxide

心血管疾病

心臟衰竭，中風，心肌梗塞

取得水困難，如老年人或中風的病人

不明原因大約25%

神經學表現

比糖尿病酮酸血症常見

幻覺，嗜睡，陽性Babinski' 徵象， 局部徵象，半邊麻痺，肌肉陣攣，眼睛震顫等

昏迷 (滲透壓通常 > 350mOsm/ Kg H2O)

癲癇 25%

治療

1.體液補充治療- 基本上體液需要每公斤150ml 或 7-9L or大約體重15%

2.一開始先給生理鹽水，以每小時1 L 的速度直到血管內體積恢復後，接著給予0.45%鹽水來矯正水分喪失，其中一半在前12小時補充，另外一半在另24小時補充，通常在二至三天內需要7 到 9 升

3.當血糖治療至低於250mg/dl時 ，靜脈點滴內需含有葡萄糖

4.在老年人、心臟衰竭、心肌梗塞、腎功能不全的病人，給予體液補充時需特別小心

電解質處理

1. 鉀離子補充須在尿液開始產生時和鉀離子正常時就要開始

2. 鉀離子補充開始由20-40mEq/L,慢慢在數天內完成

3. 其他準則與糖尿病酮酸血症相同

胰島素治療

先給初始劑量短效胰島素(RI) 10U ，再以每小時每公斤0.1-0.15 U短效胰島素(RI)持續給予，於血糖穩定後，改成皮下注射中長效胰島素(NPH)。

低血糖之處理

(3)Hypoglycemia management in diabetes mellitus

1..低血糖,先請病人食用10-15公克糖類,如低血糖症狀於15分鐘內仍無好轉,病人再食用10-15公克糖類一次。如病人已有意識不 清,應迅速給予靜脈注射,並給予50%葡萄糖2支及保持10%葡萄糖點滴注射,密切追蹤血糖直到大於100 mg/dl 為止.

2.如病人原本是服用口服降糖藥,應先停止。這段期間的血糖控治應轉為胰島素為主。

3.如病人原本是使用胰島素注射,且這時已恢復進食則飯前胰島素仍需注射,但注射量可減少至平常量的1/2至3/4 。

4.請持續密切追蹤血糖變化。此外應查明有無腎功能不全或肝功能不全, 心臟衰竭, 感染或其他會加重低血糖之問題

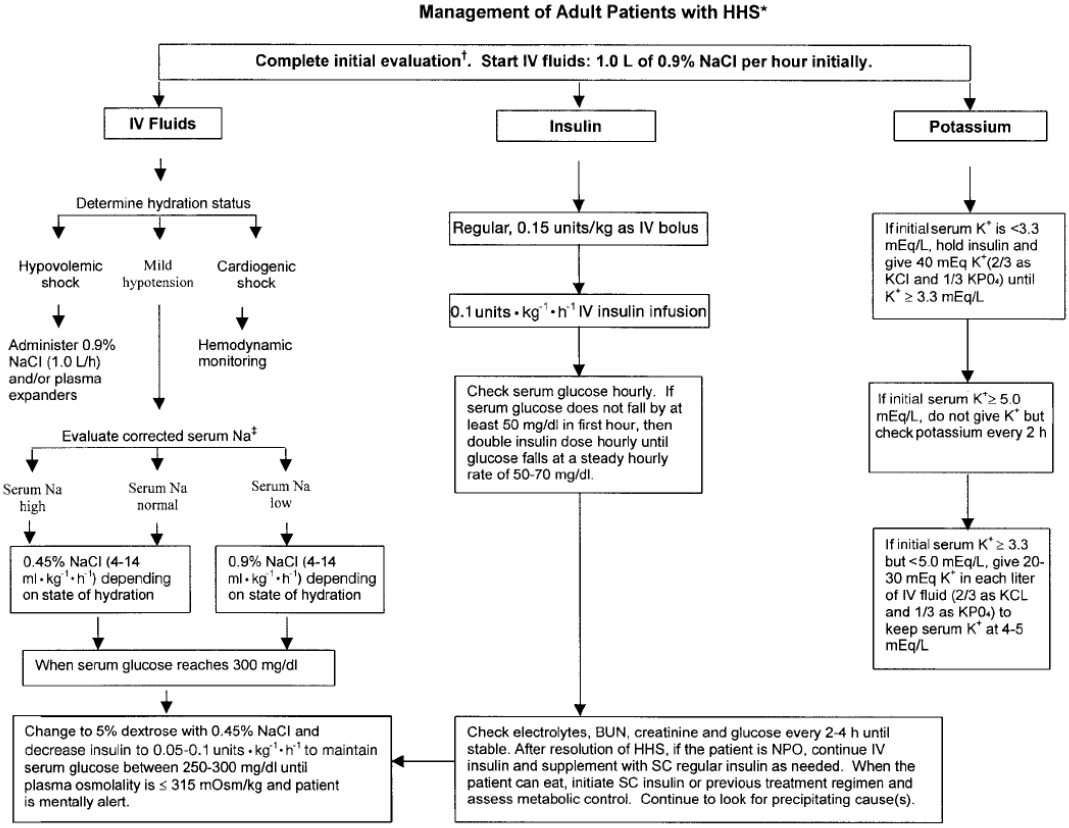


Figure 2—*Protocol for the management of adult patients with HHS. *Diagnostic criteria: blood glucose >600 mg/dl, arterial pH >7.3, bicarbonate >15 mEq/l, mild ketonuria or ketonemia, and effective serum osmolality >320 mOsm/kg H_2O. This protocol is for patients admitted with mental status change or severe dehydration who require admission to an intensive care unit. For less severe cases, see text for management guidelines. Normal ranges vary by lab; check local lab normal ranges for all electrolytes. Effective serum osmolality calculation: 2[measured Na (mEq/l)] + glucose (mg/dl)/18. †After history and physical examination, obtain arterial blood gases, complete blood count with differential, urinalysis, plasma glucose, blood urea nitrogen (BUN), electrolytes, chemistry profile, and creatinine levels STAT as well as an electrocardiogram. Obtain chest X-ray and cultures as needed. ‡Serum Na should be corrected for hyperglycemia (for each 100 mg/dl glucose >100 mg/dl, add 1.6 mEq to sodium value for corrected serum value). IV, intravenous; SC subcutaneous.*

七、高血脂肪之診斷與治療

一、簡介

A. 脂蛋白的結構可分為外層和內層，依按密度來分，由輕至重，或顆粒由大而小，可分為

(1)乳糜微粒(chylomicrons）：密度最輕、顆粒最大。

(2)極低密度脂蛋白(VLDL,very low density lipoprotein)：主要為三酸甘油酯。

(3)中密度脂蛋白(IDL,Intermediate density lipoprotein)：主要為三酸甘油酯。

(4)低密度脂蛋白(LDL,low density lipoprotein)：主要為膽固醇。是不好的膽固醇，它容易造成血管硬化，如冠狀動脈心臟病。由生理之觀點來看低密度脂蛋白並非不好，它有其正常的生理功能，只是當低密度脂蛋白太多超過身體的代謝能力等，就會沈積在血管壁，而造成血管硬化。

(5)高密度脂蛋白(HDL,high density lipoprotein)：是好的脂蛋白，扮演血管中的清道夫角色，能夠清除血管中沈積的膽固醇。

(6)脂蛋白a (Lp(a),稱為Lp little a 或 small a)：臨床上發現血液中脂蛋白a 濃度愈多，容易造成血栓形成，易造成急性心肌梗塞。

B. 表面蛋白(Apoprotein)，分為A、B、C、D、E等。

(1)表面蛋白A-I(ApoA-I)：高密度脂蛋白上佔最多。

(2)表面蛋白B(ApoB)：低密度脂蛋白上佔最多，所以血中測得表面蛋白B愈多，即表示低密度脂蛋白顆粒愈多。

C. 脂蛋白的代謝分為外源性及內源性：

a、外源性(Exogenous pathway)：

主要與食物中的來源有關，食物中的脂肪有兩類，即膽固醇及脂肪酸。

1.在臺灣，平均每人每天攝取膽固醇約0.5g（一個蛋黃約250—300㎎膽固醇）。攝取脂肪酸約100g～150g。食入的膽固醇與脂肪酸，經腸子吸收變成乳糜微粒，進入全身循環系統，受到脂蛋白脂解酶(Lipoprotein lipase,LPL)作用將乳糜微粒上的TG中的脂肪酸切下來，而切下來的脂肪酸於不同的組織有不同的用途，如在腦中，切下來的脂肪酸供腦細胞的修補作用；哺乳的母親則供作乳汁的來源；骨骼肌的細胞中，當作肌肉的能量來源。被切掉脂肪酸的乳糜微粒比較小，稱做乳糜微粒殘體(chylomicron remnant)，才回到肝臟裡去。所以，一個人吃的膽固醇或脂肪酸多時，超過低密度脂蛋白的代謝能力，血中乳糜微粒或乳糜微粒殘體堆積得多，這個人血中的三酸甘油酯就很高。

b、內源性(Endogenous pathway)：

身體內，一天所需的膽固醇（合成體內很多細胞與賀爾蒙重要來源）約1500㎎-2000

mg，其中三分之一(500㎎)是從食物中攝取，另三分之二則由肝臟製造。肝臟製造的膽固醇主要以極低密度脂蛋白的型式釋放出。進入全身循環，經脂蛋白脂解腖作用，切下極低密度脂蛋白內的脂肪酸後稱中密度脂蛋白。中密度脂蛋白一部份回到肝臟，一部份變成低密度脂蛋白。低密度脂蛋白雖不好，但它在體內有其正常的生理作用。低密度脂蛋白把肝所製造的膽固醇送到肝外需要膽固醇的組織，如腎上腺,睾丸,卵巢供合成腎上腺或性賀爾蒙所需，只是，血中低密度脂蛋白太多易沈積在血管內造成動脈血管硬化。

c. 高密度脂蛋白，來源有二，由肝臟製造或由小腸製造。作用是扮演清道夫的角色，把血管內的或肝外組織裡過多的膽固醇攜帶回肝臟。

抽血檢查中，最常檢驗的是總膽固醇和總三酸甘油酯：

(1)總膽固醇(Total cholesterol)，是由"乳糜微粒+極低密度脂蛋白+低密度脂蛋白+高密度脂蛋白"中的膽固醇所構成，其中以低密度脂蛋白內之膽固醇佔最多，約70％。所以，粗略的說總膽固醇高，大概可以反應出低密度脂蛋白膽固醇也高。但有特殊情況，如年輕運動員的總膽固醇高，若是因為其高密度脂蛋白佔的比例較多所造成的，則不須治療。

(2)總三酸甘油酯(Total triglyceride)，也是由乳糜微粒+極低密度脂蛋白+低密度脂蛋白+高密度脂蛋白"中的三酸甘油酯所構成所組成，而以極低密度脂蛋白為主佔55％。

(3)抽血檢驗總膽固醇和總三酸甘油酯時，膽固醇不隨食物而影響，隨時都可測量，不須空腹，但三酸甘油酯會受食物影響，所以測三酸甘油酯，最好空腹12-14hrs測才標準。

二、高脂血症之分類

A. 早期世界衛生組織(WHO)將高脂蛋白血症(hyperlipoproteinemia ）分為五種型，臨床上以 第Ⅱa型、第Ⅳ型較常見。

（1） 第I型(Type I) 是脂蛋白脂解腖缺少(LPL deficiency或 Apo CII deficiency) ，是過多的乳糜微粒。

（2） 第Ⅱ型分為Ⅱa、Ⅱb其中以Ⅱa較常見，以膽固醇高為主，是過多的低密度脂蛋白。Ⅱb則是膽固醇和三酸甘油酯皆高，是過多的低密度脂蛋白及極低密度脂蛋白。

（3） 第Ⅲ型以三酸甘油酯為主，其中脂蛋白以極低密度脂蛋白為主。是過多的乳糜微粒殘體及中密度脂蛋白。

（4） 第IV型以高三酸甘油酯為主，是過多的極低密度脂蛋白，糖尿病患者最常合併的血脂異常。

（5） 第Ⅴ型是)第I型加第IV型，是過多的乳糜微粒及極低密度脂蛋白。

B. 美國的分類是由美國國家膽固醇教育計畫(NCEP, National Cholesterol Education Program)所建議。

（1）總膽固醇分成三個等級。

a. <200 mg/dl: 適當

b.200～239 mg/dl：邊緣性偏高

c.>240 mg/dl：偏高

（2）高密度脂蛋白膽固醇只有下限， 40㎎／dl以上才正常，但有人認為男女有別，女性天生高密度脂蛋白膽固醇就比較高，故45㎎／dl以上才算正常。

美國國家膽固醇教育計畫又依據低密度脂蛋白膽固醇在血中濃度的高低來分類

(1)＜100 mg/dl：理想

(2)100-129 mg/dl：適當

(3)130-159 mg/dl：邊緣性偏高

(4)160-189 mg/dl：偏高

(5)≧190 mg/dl：非常高

Friedewald's 公式: 低密度脂蛋白膽固醇(mg/dl)= 總膽固醇–高密度脂蛋白膽固醇-總三酸甘油酯/5 (但總三酸甘油酯＞400㎎／dl時，則預測值會不準)。

C. 歐洲動脈硬化協會(EAS,European Atherosclerosis Association)之分類， 也是衛生署保健處建議之分類

1. 高膽固醇血症 (hypercholesterolemia): 總膽固醇 ≧ 200 mg/dl, 總三酸甘油酯＜200 mg/dl.

2. 高三酸甘油酯血症 (hypertriglyceridemia): 總膽固醇＜200 mg/dl, 總三酸甘油酯≧200 mg/dl

3. 混合型高脂血症 (mixed hyperlipidemia): 總膽固醇≧200 mg/dl and 總三酸甘油酯≧200 mg/dl.

D. 高三酸甘油酯血症之分類

分類 總三酸甘油酯 (mg/dl)	分類	疾病
＜150	正常	冠狀動脈疾病
150-199	邊緣性偏高	冠狀動脈疾病及胰臟炎
200-499	偏高	胰臟炎
≧500	非常高	

From ATP III, NCEP. JAMA 285: 2486, 2001

三、高脂血症(hyperlipidemia)之治療

臨床上，診斷高脂血症可分成原發性（Primary,因基因，環境因素所致）和續發性(Secondary，因其它原因所致）所致。

依美國國家膽固醇教育計畫之建議高脂血症可依下述方法評估

危險因子和治療準則 影響低密度脂蛋白膽固醇之主要危險因子

陽性危險因子

年齡（男性≧ 45 歲；女性≧ 55 歲）

家族遺傳史（男性＜ 55歲；女性＜ 65歲前發生冠狀動脈疾病）

抽煙

高血壓（血壓≧140/90 mmHg 或使用降血壓藥物治療者）

高密度脂蛋白膽固醇(HDL)偏低＜40 mg/dl

陰性危險因子

高密度脂蛋白膽固醇≧60 mg/dl：若存在,陽性危險因子計算方式要減一

From ATP III, NCEP. JAMA 285: 2486, 2001

A. 一般的治療原則：強調先以非藥物療養，即

(1)飲食

(2)運動

(3)減重

(4)戒煙

來治療高血脂症，而把藥物治療放在後面。經由飲食控制和運動約可以降低10％～15％的血脂 高血脂症的飲食治療

營養成分	建議攝取量
總脂肪	25-35% 總卡路里
脂肪酸	小於 7% 總卡路里
飽和	最多10% 總卡路里
多鏈不飽和	最多20% 總卡路里
單鏈不飽和	50-60% 總卡路里
醣類	15% 總卡路里
蛋白質	小於200 mg/day
膽固醇	到達並維持理想體重
總卡路里	

From ATP III, NCEP. JAMA 285: 2486, 2001

低密度脂蛋白膽固醇：治療的主要標的

由動物實驗、實驗室研究、流行病學以及高膽固醇血症的基因形式等種種研究皆指出低密度脂蛋白膽固醇的升高是引起冠心症的主要因素。此外，最近的臨床試驗確切地顯示出降低低密度脂蛋白膽固醇的治療可以降低冠心症的風險。ATP III 持續認同降低低密度脂蛋白膽固醇為降低膽固醇治療的首要目標。所以，治療之主要目標及開始治療的分界點，皆以低密度脂蛋白膽固醇來表示。

在不同風險病患族群中,低密度脂蛋白膽固醇的分界點及治療的起始點 病人分類	低密度脂蛋白膽固醇		
風險程度	**目標值(mg/dl)**	**需採用治療性生活型態改變(mg/dl)**	**開始藥物治療(mg/dl)**
超高風險：急性冠狀動脈症候群、冠狀動脈疾病合併多項風險因子或代謝症候群	<70	≧100	≧100
高風險：冠心病或與冠心病同等風險**或兩個以上風險因子合併** 10 年的風險度>20%	<100	≧100	≧100
中高風險：兩個以上的危險因子**合併** 10 年的風險度 10%~20%	<130 (**理想**：<100)	≧130	≧130
中度風險：兩個以上的危險因子**合併** 10 年的風險度≦10%	<130	≧130	≧160
低度風險：0-1 個危險因子	<160	≧160	≧190 (160-189 依情況而定)

註* 冠心病風險同義字包括：中風、周邊動脈疾病、腹主動脈瘤、糖尿病等

From ATP III, NCEP. JAMA 285: 2486, 2001.

降低低密度脂蛋白膽固醇的附加價值：以代謝症候群爲治療的次要標的

證據顯示藉由降低低密度脂蛋白膽固醇治療以外的方法修正其他危險因素時，可降低冠心症的風險。治療的潛在次要目標之一為代謝症候群，它代表代謝器官匯集的脂質及非脂質危險因素。此一症狀與廣義的代謝異常-胰島素抗性-有密切關聯。胰島素抗性為胰島素的正常作用受到損傷。過多的身體脂肪(特別是異常肥胖）和缺乏體能活動，促進了胰島素抗性，但也有些人是因在基因方面易於患胰島素抗性。

代謝症候群的危險因素具高度一致性；總計起來，它們對任何程度的低密度脂蛋白膽固醇，皆有加強冠心症風險的作用。當下表的三個或以上的危險決定因素出現時，可診斷為代謝症候群。 代謝症候群的臨床定義

危險因子	定義範圍
腹部肥胖（腰圍）	
男性	> 102 cm (40 inch) [東方人：> 90 cm]
女性	> 88 cm (35 inch) [東方人：> 80 cm]
三酸甘油脂	> 150 mg/dl
高密度脂蛋白膽固醇	
男性	< 40 mg/dl
女性	< 50 mg/dl
血壓	≧130/≧85 mmHg
空腹血糖	≧100 mg/dl

處理代謝症候群有二重目的：（1）降低潛在的原因（如肥胖和缺乏體能活動）和（2）治療相關的非脂質及脂質危險因素。

處理代謝症候群的潛在原因

與代謝症候群相關的所有脂質與非脂質危險因素的第一線治療，為減輕體重和增加體能活動，如此將有效降低所有危險因素。因此適當控制低密度脂蛋白膽固醇後，若有代謝症候群時，治療性生活型態改變應著重於減輕體重和增加體能活動。

體重控制

ATP III認為超重和肥胖是冠心症的主要潛在危險因素及主要標的。降低體重可加強低密度脂蛋白膽固醇之降低，並減少所有代謝症候群的危險因素。

體能活動

缺乏體能活動也是冠心症的主要潛在危險因素。它加強了代謝症候群的非脂質及脂質危險因素。它還會進一步損害心血管健康及冠狀動脈血流。規律的體能活動可降低極低密度脂蛋白膽固醇以及提升高密度脂蛋白膽固醇，且對某些人而言亦可降低低密度脂蛋白膽固醇。它也可以降低血壓、降低胰島素抗性、並適宜地影響心血管功能。因此，ATP III建議規律的體能活動列為處理高膽固醇的例行要素。

脂質及非脂質危險因素的特別治療

除了潛在的危險因素，直接治療代謝症候群的脂質及非脂質危險因素將可降低冠心症風險。這包括治療高血壓，讓冠心症患者服用阿司匹靈，以降低血栓前狀態，以及治療高三酸甘油脂與低高密度脂蛋白膽固醇。

降血脂用藥，分爲降膽固醇和降三酸甘油酯兩類。

第一種：Fibric Acid derivatives (fibrate, fibric acids)：Bezafibrate, Ciprofibrate, Fenofibrate, Gemfibrozil 等.

作用：降低三酸甘油酯進而使高密度脂蛋白膽固醇升高(因兩者關係常相反)。機轉：可促進脂蛋白脂解脢(Lipoprotein Lipase)的活性，所以減少了三酸甘油酯，另外這種藥也可抑制極低密度脂蛋白從肝臟釋放出來，有的使用後會造成肌肉酸痛、發炎。

第二種：Nicotinic Acid 及其衍生物 : Acipimox

為維生素 B 群的一種，用來治療癩皮症，後來發現可以降三酸甘油酯和膽固醇。機轉：抑制脂肪組織分解出脂肪酸，脂肪酸就不能回肝臟，肝臟制造三酸甘油酯的材料就不足，極低密度脂蛋白就無法製造了。副作用：吃藥後半小時內因為血管擴張，所以全身發熱發燙，但接下來幾天會漸漸改善。尿酸增加。胃酸增加，消化道潰瘍機會略加重。糖尿病人的血糖會略升。

第三種：Colestipol (5-30 g/day) and Cholestyramine (4-24 g/day)，為一包一包的粉狀樹酯。機轉：抑制腸肝循環(enterohepatic circulation)。正常情況下，由膽管排出的膽酸到迴腸末段之後，被重吸收回肝臟,用來製造膽固醇。此種藥物服用後，會和腸道中的膽酸結合而隨糞便排出，這使得腸肝循環的功能減少，但肝臟還是要製造膽固醇。這時它會增加自己肝細胞表面的低密度脂蛋白接受器，使循環中的低密度脂蛋白膽固醇被肝臟回收，而降低血中的膽固醇。副作用：便秘。

第四種：HMG CoA reductase inhibitor (statin): Lovastatin, Pravastatin, Simvastatin, Fluvastatin, Atorvastatin, Cerivastatin, Rosuvastatin 等.

機轉：HMG CoA 還原脢是肝內自製膽固醇的速率限制酵素，而 statin 這類藥能抑制此酵素，使肝臟不能自製膽固醇，但肝臟仍需要膽固醇來製造膽酸，只好代償性地增加肝臟細胞表面的低密度脂蛋白接受器，以回收循環中的低密度脂蛋白，進而降低血中的膽固醇。效果很好，可降低總膽固醇達 30～35%，而低密度脂蛋白膽固醇可降低達 35～40%。副作用：1.暫時性之肝功能異常 2.肌肉酸痛，肌炎，尤其是在和 fibrate 或免疫抑制藥 cyclosporine 合用時。如果吃藥之後病患的 creatine kinase 快速上昇時就要趕快停藥。最近發現大劑量之 statin 亦可降三酸甘油酯，當三酸甘油酯濃度愈高降三酸甘油酯作用愈明顯。

附錄: Framingham 10 年冠心病風險評估表

一. 年齡

年齡(歲)	分數	
	男性	女性
20-34	-9	-7
35-39	-4	-3
40-44	0	0
45-49	3	3
50-54	6	6
55-59	8	8
60-64	10	10
65-69	11	12
70-74	12	14
75-79	13	16

二、總膽固醇

總膽固醇 (mg/dl)	分數 (男性)				
	20-39 歲	40-49 歲	50-59 歲	60-69 歲	70-79 歲
<160	0	0	0	0	0
160～199	4	3	2	1	1
200～239	7	5	3	1	0
240～279	9	6	4	2	1
≧280	11	8	5	3	1

總膽固醇 (mg/dl)	分數 (女性)				
	20-39 歲	40-49 歲	50-59 歲	60-69 歲	70-79 歲
<160	0	0	0	0	0
160～199	4	3	2	1	1
200～239	8	6	4	2	1
240～279	11	8	5	3	2
≧280	13	10	7	4	2

三、吸煙

	分數 (男性)				
	20-39 歲	40-49 歲	50-59 歲	60-69 歲	70-79 歲
非吸煙者	0	0	0	0	0
吸煙者	8	5	3	1	1

	分數 (女性)				
	20-39 歲	40-49 歲	50-59 歲	60-69 歲	70-79 歲
非吸煙者	0	0	0	0	0
吸煙者	9	7	4	2	1

四、高密度脂蛋白膽固醇

高密度脂蛋白膽固醇 (mg/dl)	分數	
	男性	女性
≧60	-1	-1
50～59	0	0
40～49	1	1
＜40	2	2

五、收縮壓

收縮壓(mmHg)	男性		女性	
	無治療者	治療者	無治療者	治療者
<120	0	0	0	0
120～129	0	1	0	3
130～139	1	2	1	4
140～159	1	2	2	5
≧160	2	3	3	6

六、10 年內冠心病風險評估表

男性		女性	
總分數	10 年內風險(%)	總分數	10 年內風險(%)
<0	<1	<9	<1
0	1	9	1
1	1	10	1
2	1	11	1
3	1	12	1
4	1	13	2
5	2	14	2
6	2	15	3
7	3	16	4
8	4	17	5
9	5	18	6
10	6	19	8
11	8	20	11
12	10	21	14
13	12	22	17
14	16	23	22
15	20	24	27
16	25	≧25	≧30

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糖尿病尿病與高血脂症

一、前言

糖尿病患罹患心臟血管疾病的機會比非糖尿病患高出二至四倍，雖然長期高血糖可能是部份原因，但是糖尿病患合併之血脂異常，顯然扮演十分重要的角色。對第一型糖尿病患而言，如果血糖控制不佳，常見極低密度脂蛋白（very low density lipoprotein，簡稱 VLDL）昇高，但在胰島素控制後則很快可以改善，主要是因胰島素增強脂蛋白脂解酶（lipoprotein lipase）之活性進而加速分解 VLDL，同時控制良好的第一型糖尿病患其高密度脂蛋白（high density lipoprotein，簡稱 HDL）膽固醇反而較高。

在第二型糖尿病患其血脂異常，主要是 VLDL 增加所以三酸甘油脂增加，但高密度脂蛋白膽固醇卻下降（三酸甘油脂濃度與高密度脂蛋白膽固醇有很好的反比關係），至於低密度脂蛋白（low density lipoprotein 簡稱 LDL）膽固醇濃度與非糖尿病患差不多，但其低密度脂蛋白顆粒較小、密度較實，有人發現此種低密度脂蛋白顆粒一方面較易被氧化，一方面也容易進入血管內壁形成動脈粥狀硬化。至於 LP(a)之濃度在糖尿病患與非糖尿病患之比較也無明顯差異。

二、病理生理學

糖尿病患者之三酸甘油脂增多與胰島素阻抗性(insulin resistance)有密切之關係，因為胰島素阻抗性使脂肪細胞分解之脂肪酸（free fatty acid）增加，這些脂肪酸回到肝臟加上胰島素之作用會促使 VLDL 分泌增多，同時因為脂蛋白脂解酶之活性變差也使 VLDL 不容易被代謝分解。VLDL 上的三酸甘油脂與 HDL 上的脂化膽固醇互相交換使 HDL 上的三酸甘油脂增多，易受到肝臟脂解酶（hepatic lipase）之分解所以 HDL 就減少了。

三、治療

依美國糖尿病學會（American Diabetes Association, ADA）及美國心臟病學會（American Heart Association, AHA）之建議在糖尿病患其 LDL 膽固醇、HDL 膽固醇及三酸甘油脂之危險因子，可分為高、中及低三個程度，不管有沒有心臟血管或周邊血管之疾病，其 LDL 膽固醇之治療目標最好定在＜100mg/dl（有人認為如果沒有這些大血管疾病可以定在＜130mg/dl，最近 Haffner 等人也在芬蘭研究發現糖尿病患即使沒有冠心症七年後得到冠心症機會與無糖尿病差不多。

治療方面第一步仍考慮把血糖控制下來，以飲食控制、規則運動、把體重維持在標準之內，但對三酸甘油脂大於 400mg/dl 者可考慮直接給予藥物。對 LDL-C 高者 statin 類仍是第一選擇，對三酸甘油脂高者 fibric acid（如 gemfibrozil）是第一選擇。最近我們的研究資料顯示 gemfibrozil 亦可改善血管之凝固功能。

四、結論

目前並無專對糖尿病所做之大型前瞻性流行病學研究來探討降血脂藥物到底能否減少心臟血管疾病，但是根據過去所做的 Helsinki Heart Study（gemfibrozil），4S（simvastatin）及 CARE（pravastatin）發現改善血脂肪對糖尿病患一樣有效，可以

推論積極祇療高血脂症確可減少糖尿病之心臟血管疾病。

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八、低血糖診斷及處理

Definition

Whipple's triad:

1. Symptoms and signs of hypoglycemia.
2. Plasma glucose 45mg/dl or less.
3. Reversibility of symptoms and signs after glucose administration.

Causes of hypoglycemia

Fasting

Drugs

Especially insulin, sulfonylureas, ethanol

Sometimes pentamidine, quinine

Rarely: salicylates, sulfonamides

Possible: ACEI, beta-blockers, indomethacin, acetaminophen, colchicine, penicillamine, ketoconazole, clofibrate, bezafibrate, haloperidol

Endogenous hyperinsulinism

Insulinoma, other ß cell disorders

Secretagogue (sulfonylurea)

Autoimmune (autoantibodies to insulin, insulin receptor, ß cell?)

Ectopic insulin secretion

Critical illnesses

Hepatic, renal, or cardiac failure

Sepsis, starvation

Endocrine deficiencies

Cortisol(adrenal insufficiency), growth hormone deficiency, hypothyroidism, hypopituitarism.

Non-ß-cell tumors

Fibrosarcoma, mesothelioma, rhabdomyosarcoma, liposarcoma, other sarcoma

Hepatoma, adrenocortical tumors, carcinoid

Leukemia, lymphoma, melanoma, teratoma

Disorder of infancy or childhood

Inherited enzyme defects

Infants of diabetic mothers (hyperinsulinism)

Persistent hyperinsulinemic hypoglycemia of infancy

Factitious

Insulin, sulfonylureas

Nonfasting (postprandial)
Alimentary or Reactive: after gastric surgery, occur 1-2 hrs after meal.
Mechanism:
too rapid glucose absorption, resulting in a robust insulin response.
Functional: occur 3-5 hrs after meal, eg: IGT
Symptoms of hypoglycemia
I. Adrenergic stage – autonomic or neurogenic symptoms (usually when plasma glucose < 60mg/dl): palpitation, sweating, hunger, tremor, tachycardia
II. Neuroglycopenic stage (usually when BS< 50mg/dl):
lethargy, drowsiness, bezarre behaviour, seizure, coma
Hypoglycemia unawareness
Defective glucose counterregulation with a blunting of autonomic symptoms and counterregulatory hormone secretion during hypoglycemia.
Hypoglycemia unawareness may develop in patients who are:

甲、undergoing intensive diabetes therapy
乙、taking beta-blocker
丙、frequently in hypoglycemic stage
丁、have diabetic neuropathy with autonomic dysfunction

These patients should be encouraged to monitor their blood glucose frequently and take timely measures to correct low values (<60 mg/dl). In patients with very tightly controlled diabetes, slight relaxation in glycemic control and avoidance of hypoglycemia can restore the lost warning symptoms.
Counterregulatory response to hypoglycemia
1. Glucagon is the key hormone affecting recovery from hypoglycemia.
2. Adrenergic-catecholamine response represent the subsequent back-up system of recovery from hypoglycemia.
Treatment
1. In alert patients, oral carbohydrate 15-20gm should be given immediately, such as
1 cup of milk(8oz), 4oz juices, cookies and candy bars. Hypoglycemia associated with acarbose therapy should preferentially be treated with glucose.
2. In patients with restricted oral intake or impaired mentality, 50% glucose 20-50ml should be given via iv bolus immediately, followed by 5-10% glucose water iv infusion to maintain BS > 100mg/dl.
3. If symptoms not improve, step 1 and 2 should be repeated every 10-15 min till hypoglycemic symptoms reversed.

4. Glucagon 1 mg IM (or SC) can be given to treat severe hypoglycemia in patient with impaired mentality or in whom iv access cannot be secured immediately. Vomiting is a frequent side effect, care should be taken to prevent the risk of aspiration.
5. Frequent small meals with reduced carbohydrate content may ameliorate symptoms of alimentary hypoglycemia.

Prevention

1. Glucose tablets and carbohydrate supplies should be readily available to patients with DM at all times.
2. A glucagon kit should be available to patients with a history of severe hypoglycemia, family members and roommates should be instructed in its proper use.

Insulinoma

common in 4-6th decades

10% malignant, 10% multiple

Diagnosis

1.Insulin assays, insulin/glucose ratio > 0.3 ---> high suspicion

2. 72 hours-fast test

3. Image study: CT, MRI, transesophageal ultrasound

4. Transhepatic portal vein sampling if image study fail to demonstrate lesion

Treatment

1. Operation is the treatment of choice.
2. Inoperable cases- diazoxide.

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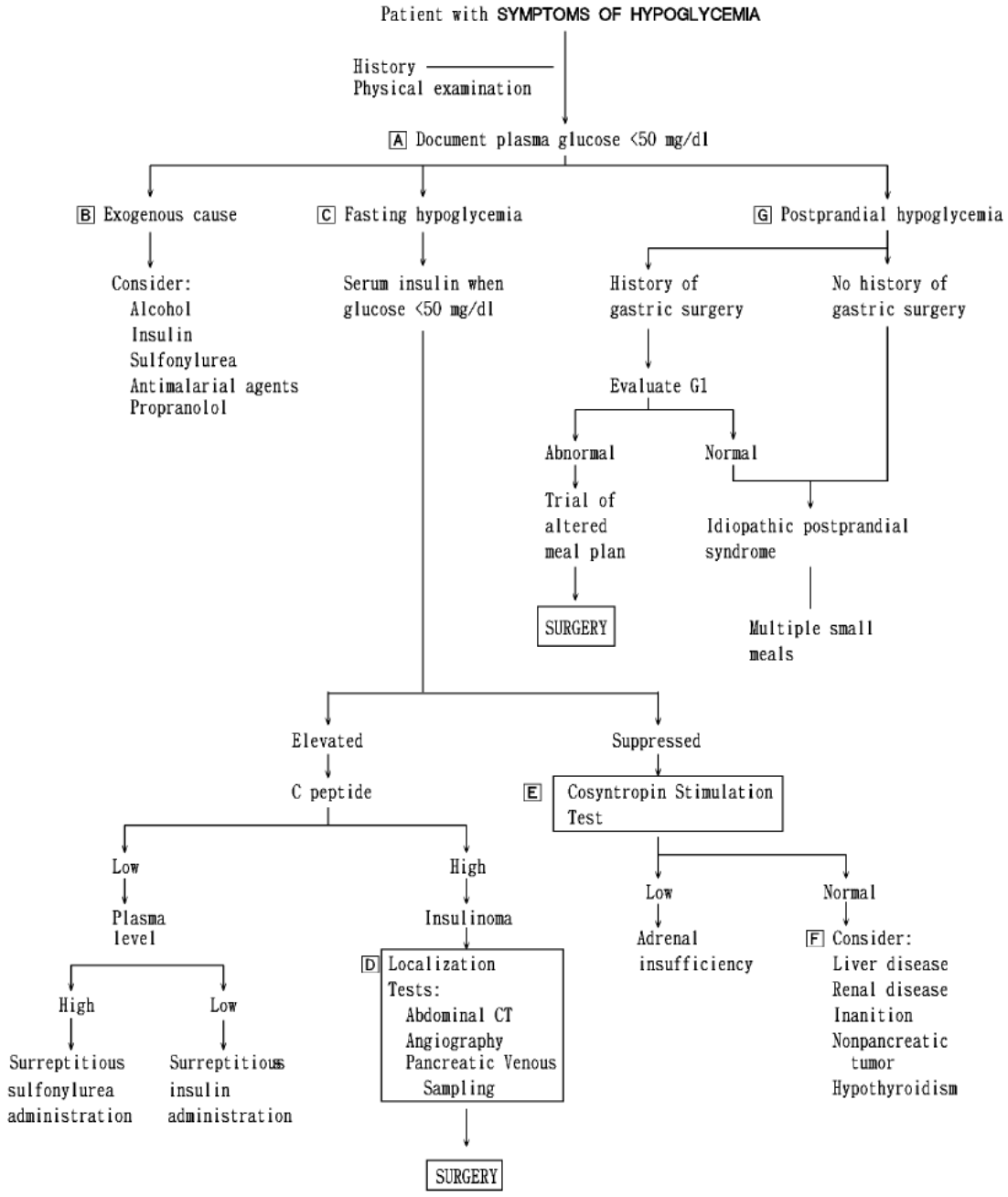

Patient with SYMPTOMS OF HYPOGLYCEMIA
History
Physical examination
A Document plasma glucose <50 mg/dl
B Exogenous cause
C Fasting hypoglycemia
G Postprandial hypoglycemia
Consider:
Alcohol
Insulin
Sulfonylurea
Antimalarial agents
Propranolol
Serum insulin when glucose <50 mg/dl
History of gastric surgery
No history of gastric surgery
Evaluate GI
Abnormal
Normal
Trial of altered meal plan
Idiopathic postprandial syndrome
SURGERY
Multiple small meals
Elevated
Suppressed
C peptide
E Cosyntropin Stimulation Test
Low
High
Plasma level
Insulinoma
Low
Normal
High
Low
D Localization Tests:
Abdominal CT
Angiography
Pancreatic Venous Sampling
Adrenal insufficiency
F Consider:
Liver disease
Renal disease
Inanition
Nonpancreatic tumor
Hypothyroidism
Surreptitious sulfonylurea administration
Surreptitious insulin administration
SURGERY

九、甲狀腺高能症

COMMON CAUSES

THYROTOXICOSIS ASSOCIATED WITH HYPERTHYROIDISM*

Production of abnormal thyroid stimulator (Graves' disease)
Intrinsic thyroid autonomy
  Toxic adenoma
  Toxic multinodular goiter

THYROTOXICOSIS NOT ASSOCIATED WITH HYPERTHYROIDISM†

Inflammatory disease
  Silent thyroiditis
  Subacute thyroiditis
Extrathyroisal source of thyroid hormone
  Exogenous hormone

UNCOMMON CAUSES

THYROTOXICOSIS ASSOCIATED WITH HYPERTHYROIDISM

Production of thyroid stimulators
  TSH hypersiecretion
  Trophoblastic tumor
  Hypermesis gravidarum

Intrinsic thyroid autonomy
  Thyroid carcinoma
  Nonautoimmune autosomal dominant hyperthyroidism
  Struma ovarii†

Drug-induced hyperthyroidism
  Iodine and iodine-containing drugs and radiographic contrast agents†

THYROTOXICOSIS NOT ASSOCIATED WITH HYPERTHYROIDISM†

Inflammatory disease
  Dryg-induced thyroiditis(amiodarone, interferon)
  Infarction of thyroid adenoma
  Radiation thyroiditis

TABLE Common Clinical Manifestations of Thyrotoxicosis

SYMPTOMS	GENERAL SIGNS
Nervousness	Hyperactivity
Fatigue	Tachycardia or atrial arrhythmia
Weakness	Systolic hypertension
Increased perspiration	Warm, moist, smooth skin
Heat intolerance	

Tremor	Stare and eyelid retraction
Hyperactivity	Tremor
Palpitation	Hyperreflexia
Appetite change (usually increase)	Muscle weakness
Weight change(usually loss)	
Menstrual disturbances	

Graves' disease:

A. Clinical features:

(1)thyrotoxicosis,(2)diffuse goiter,(3)ophthalmopathy,(4)dermopathy (localized myxedema). F:M=5:1, most prevalent in 20-40 years

B. Etiology: autoimmune disease of unknown cause, strong family predisposition

C. Auto-Ab:

(1) TSHR antibodies-disease specific, 80-100% of untreated patients with thyrotoxicosis caused by Graves' disease are positive.

(2) Tg and TPO antiboidies: 2/3 of patient are positive

TSHR antibody-for "apathetic" hyperthyroid, pregnant patients, predict of response to antithyroid drug

D. Diagnosis:

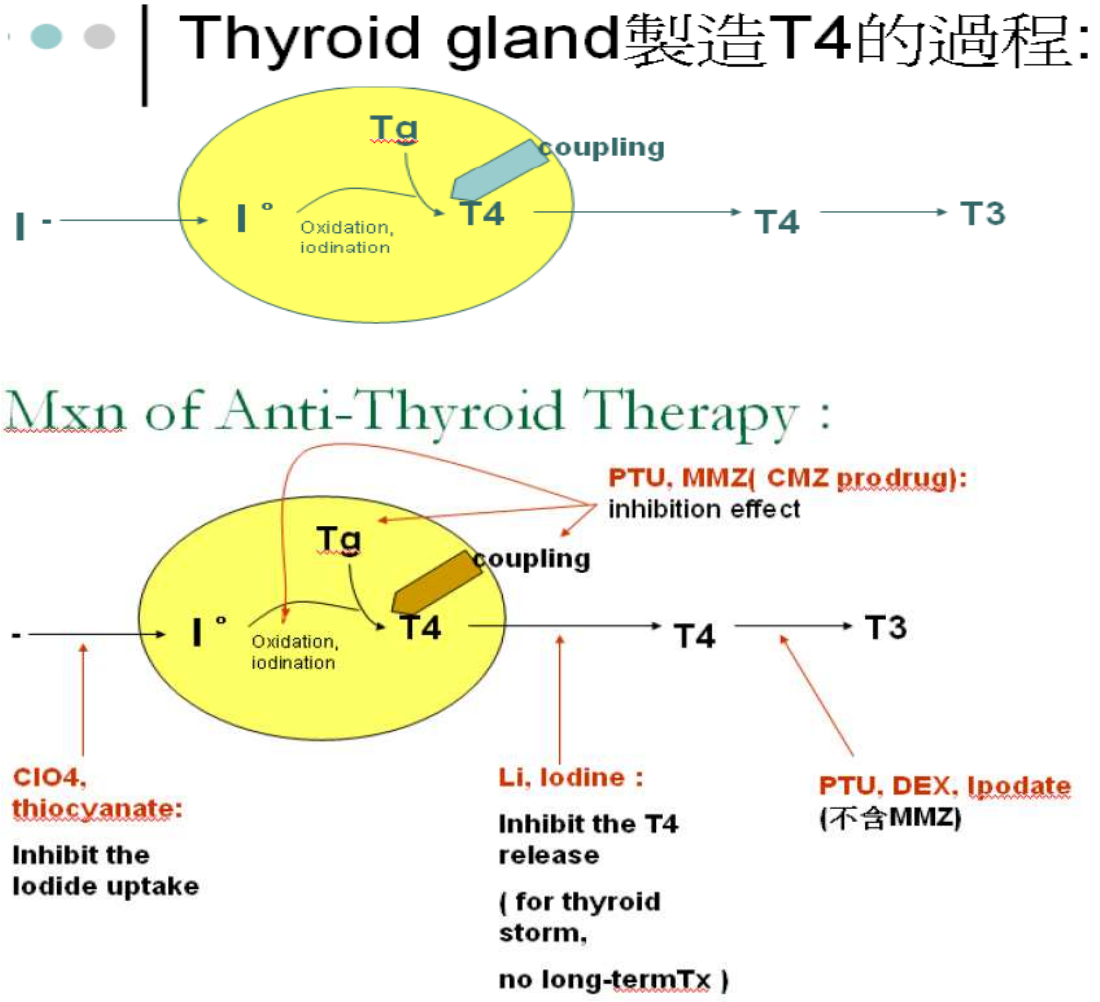
By clinical features, high T3, T4, low TSH. If dermopathy or ophthalopathy are present, the diagnosis of Graves' disease can be made without further test.

輔助診斷: auto-Ab and I131 scan(r/o functional adenoma)

E. Particular forms of Graves❼ disease:

Apathetic hyperthyroidism: older patients, present with weight loss, small goiter, slow atrial fibrillation, and severe depression.

F. Treatment



(1) Antithyroid Drugs: two classes-Thiouracil:

- propylthiouracil, 50 mg/tab.
- Imidazoles: methimazole and carbimazole, 10 mg/tab.

Mechanism of action:

A. Intrathyroidial effects: inhibition of iodine oxidation and organization, inhibition of iodotyrosine coupling.

B. Extrathyroidal effects: inhibition of conversion of T4 to T3 (PTU, but not MMI) and possible immunosuppressive

Dosage:

A. PTU 300 mg(100 mg tid) one month→100 mg bid one month→50 mg bid.

B. carbimaazoles:30 mg or 10 mg qd as initial dose

Clinical consideration:

(a) long duration of therapy: 1-2 years

(b)high relapse rate: 50%

Side effects of antithyroid drugs:

(a)Most frequent: skin rash.→antihistamine or shift to another class of drug. (b)Agranulocytosis: rare (0.5%), mostly occurs within 3 months after initiation of therapy, but even later. Presentation: fever & evidence of infection, mostly orpharynx. Management: prompt discontinue ATD, strong antibiotics.

Side Effects of Antithyroid Drugs

MINOR

Common (1-5%)
Rash
Urticaria
Arthralgia
Fever
Transient leukopenia
Uncommon(<1%)
Gastrointestinal
Abnormalities of taste and smell
Arthritis

MAJOR

Rare(0.2%-0.5%)
Agranulocytosis
Very Rare(<1%)
Aplastic anemia
Thrombocytopenia
Hepatitis(PTU)
Cholestatic hepatitis (methimazole)
Vasculitis, systemic lupus-like syndrome
Hypoprothrombinemia
Hypoglycemia(due to anti-insulin antibody) (MMZ)

Other drugs used in the treatment of thyrotoxicosis caused by Graves' disease:

(a)Inorganic iodine:Lugol's solution (3-5 drops tid) or SSKI 1 drop tid.

Mechanism: decrease iodine transport, oxidation and organification (Wolff-Chaikoff effct) and rapidly block the release of thyroid hormone.

Escape phenomenon, so should be used less than 10 days.

Indication: A.preparation for surgery. B.thyrotoxic storm. C. Adjunct after raddioiodine therapy.

(b) β-adreneergic antagonist drugs: rapidly improves the symptoms of palpitation and hand tremor.

(2) Radioactive iodine:

1. Avoided in children, contraindicated in pregnancy

2. Dose: 5-7 mCi

3. Improved after 6-8 weeks

4. Complication: hypothyroidism, the rate increase with time, 10 years after therapy-50%.

(3) Surgical therapy:

Performed in only a few circumstances: child, adolescents and pregnant women who are allergic to or noncompliant to antithyroid drugs, patiesnts with large goiters, and patients who prefer

Thyrotoxic periodic paralysis:

- Asian male /c symptoms of untreated hyperthyroidism
- Awakens at night or in the morning /c flaccid paralysis of the lower limbs and usually /c Hx of vigorous exercise or having a large high-carbohydrate meal
- May involve the arm but facial or respiratory muscle are rarely involved
- Pathogenisis: thyrotoxicosis result in increased Na-K ATPase activity with increased intracellular transport of K+
- Tx
    - Oral K+: no loss of total body K
    - B-blocker(inderal): block the b-adrenergic stimulation of Na-K-ATPase
    - Anti-thyroid drug should be started immediately
    - Avoid glucose, b-adrenergic agonist

Thyrotoxic Storm

1. Clinicl diagnosis: fever (>38.5℃), tachycardia (ot of proportion to the fever), GI dysfunction (nausea, vomiting, diarrhea and even jaundice), and CNS signs confusion to coma.

2. A history of partially treated thyrotoxicosis

The presence of precipitating factors.: infection, surgery, trauma, iodinated contrast dyes, hypoglycemia, pariturition..

3.Management :

1) high dose PTU

2) lugol solution

3) hydrocortisone

4) high dose inderol

5) symptomatic treatment for symptoms of thyroid storm

4.Dosage:

1) Propylthiouracil

- Dose: 300-400 mg Q4H
- PO, NG, or REC
- Preferable to MMZ (methimazole) due to additional action of inhibiting the peripheral generation of T3 from T4 by type 1 iodothyronine deiodinase
- Mxn: prevent enrichment of glandular hormone stores by iodine

2) SSKI or ipodate

- Mxn: Acutely retard the release of hormone from the thyroid gland.
- Dose:

SSKI:5dropsQ6H

Ipodate: 0.5 g Q12H

Sodium iodide : 0.25 g Q6H

- 投予 PTU 後 1 hr 後 給 lugol solution

(PTU should be given before iodine -- to inhibit the synthesis of additional thyroid hormones from the administered iodine).

- However, because iodine blocks release of preformed thyroid hormones from the

thyroid gland, its administration should not be delayed or omitted in the severely toxic pt if PTU is not immediately available.

3) Dexamethasone:

- High dose decadron (2 g PO Q6H)
- Mxn:

1. inhibit the release of hormone from gland and the peripheral generatino of T3 from T4

2. synergize with iodide and PTU

4)Inderol:

- Dose: 40 -80 mg Q6H

5)THERAPY TO AVOID DECOMPENSATION OF NORMAL HOMEOSTATIC MECHANISMS

Treatment of hyperthermia

Acetaminophen

Cooling

Correction of dehydration and poor nutrition

Supportive therapy

Oxygen

Vaspressors

Treatment of congestive heart failure, if present (digoxin, diuretics)

Corticosteroids

十、甲狀腺低能症

Causes of Hypothyroidism

PRIMARY HYPOTHYROIDISM

Destruction of thyroid tissue
Chronic autoimmune thyroiditis: atrophic and goitrous forms

Radiation: ^{131}I therapy for thyrotoxicosis, external radiotherapy to the neck for lymphoma or head and neck cancer

Subtotal and total thyroidectomy
Infiltrative diseases of the thyroid (amyloidosis, scleroderma)

Defective thyroid hormone Biosynthesis

Iodine deficiency

Drugs wih antitgyroid actions:lithium, iodine, iokine-containing drugs, and iodine-containing radiographic contrast agents

CENTRAL HYPOTHYROIDISM

Pituitary disease
Hypothalamic disease

TRANSIENT HYPOTHYROIDISM

Silent thyroiditis*
Subacute thyroiditis

After withdrawal of thyroid hormone therapy in euthyroid patients

Deficiency or excess of pituitary hormones other than TSH

*including postpartum tbyroiditis.

Clinical Manifestations of Hypothyroidism

SYMPTOMS

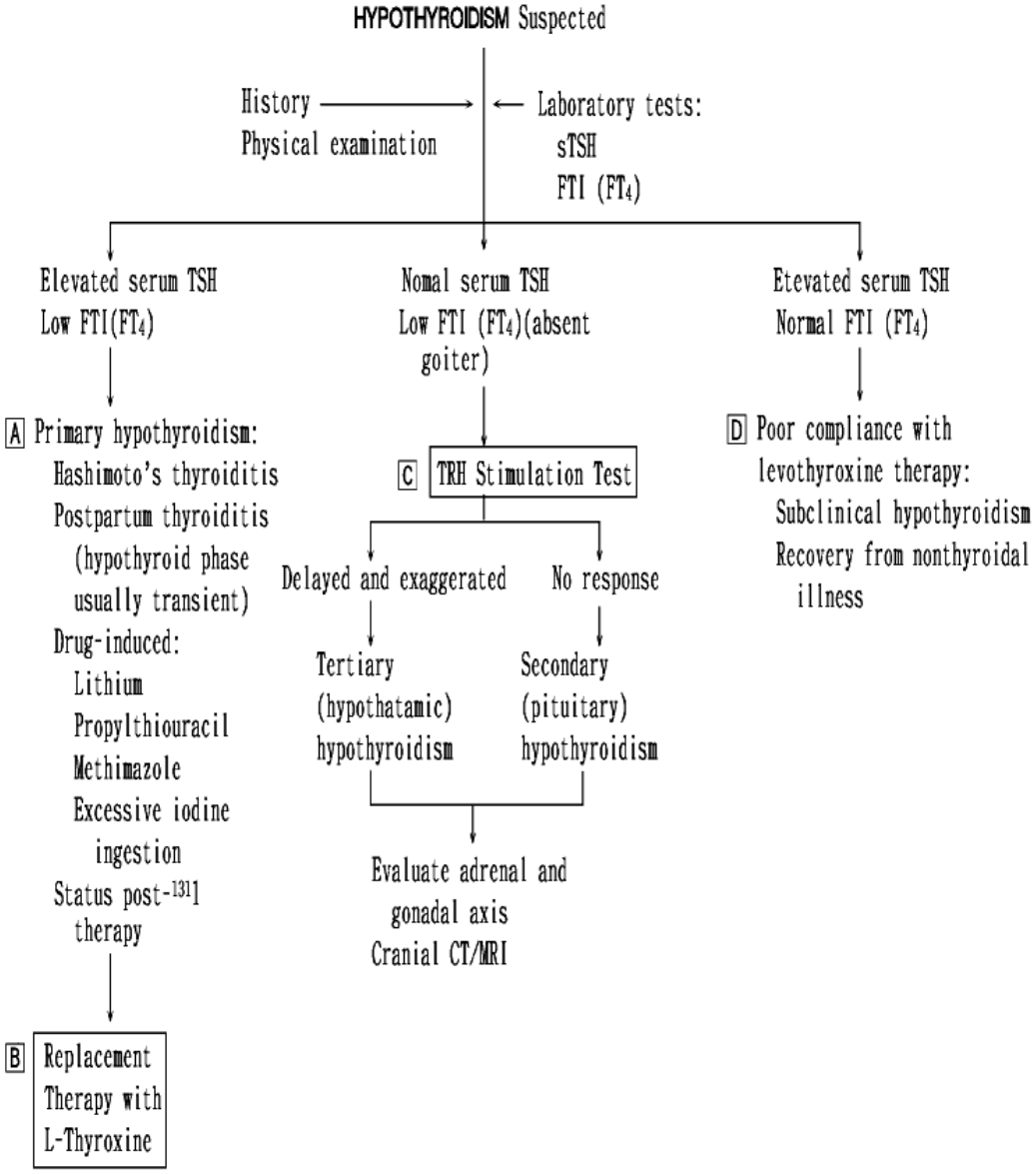
Fatigue
Lethargy
Sleepiness
Mental impairment
Depression
Cold intolerance
Hoarseness
Dry skin
Decreased perspiration
Weight gain
Decreased appetite
Constipation
Menstrual disturbances
Arthralgia
Paresthesia

SIGNS

Slow movements
Slow speech
Hoarseness
Bradycardia
Dry skin
Nonpitting edema (myxedema)
Hyporeflexia
Delayed relaxation of reflexes

SYMPTOMS AND SIGNS ASSOCIATED WITH SPECIFIC CAUSES OF HYPOTHYROIDISM

Diffuse or nodular goiter
Symptoms and signs of pituitary or hypothalamic tumor
Headache
Visual impairment


HYPOTHYROIDISM Suspected
History
Physical examination
Laboratory tests:
sTSH
FTI (FT4)
Elevated serum TSH
Low FTI(FT4)
Nomal serum TSH
Low FTI (FT4)(absent goiter)
Etevated serum TSH
Normal FTI (FT4)
A Primary hypothyroidism:
Hashimoto's thyroiditis
Postpartum thyroiditis
(hypothyroid phase usually transient)
Drug-induced:
Lithium
Propylthiouracil
Methimazole
Excessive iodine ingestion
Status post-131I therapy
C TRH Stimulation Test
D Poor compliance with levothyroxine therapy:
Subclinical hypothyroidism
Recovery from nonthyroidal illness
Delayed and exaggerated
No response
Tertiary (hypothatamic) hypothyroidism
Secondary (pituitary) hypothyroidism
Evaluate adrenal and gonadal axis
Cranial CT/MRI
B Replacement Therapy with L-Thyroxine

Myxedema coma

1. end stage of untreated hypothyroidism
2. progressive weakness, stupor, hypothermia, hypoglycemia, hyponatremia, water intoxication and death
3. mortality is high
4. Hx of thyroid disease, radioiodine therapy, or thyroidectomy
5. Precipitating factors: heart failure, pneumonia, pulmonary edema, sedative or narcotic
6. Presentation: bradycardia, marked hypothermia. Usually an obese elderly woman with yellowish skin, a hoarse voice, a large tongue, thin hair, puffy eyes, ileus, and slow reflexes
7. Lab. Data: high serum carotene, elevated cholesterol, CK and LDH; increased CSF protein.

Treatment:

1. mechanical ventilation may be necessary
2. underlying disease
3. avoid excessive free water intake
4. levothyroxine iv loading 300-400 ug→ 50 ug/day
5. consider adrenal insufficiency before thyroxine-hydrocortisone 50 mg q6h
6. in older or with CAD—start from low dose

十一、甲狀腺結節處理

針對甲狀腺結節的臨床處理，已有很多篇文章探究，第一步一般是先驗甲狀腺促素(TSH)的濃度。若TSH偏低，則建議作放射碘掃描排除掉熱結節或葛瑞夫茲氏病(Graves'disease)，再為表現為冷或溫結節者作細針抽吸切片。因為幾乎所有的功能性結節都是腺瘤(adenoma))，切片便不需要，除非有其他臨床表現懷疑是惡性，如快速成長或結節內有低功能區。

唯一要注意的是，已不建議用鎵-99m(Tc-99m)甲狀腺掃描作甲狀腺結節的影像評估，因為有3-8%患者在鎵-99m掃描下呈現熱結節，但再作放射碘掃描，反而呈現非功能性,而有惡性的可疑。

至於TSH正常或偏高的結節，連同上述TSH低下且排除熱結節者，則一律作細針穿刺切片。細針穿刺切片檢查的結果，不外乎良性、惡性、無法判定(indeterminate) / 懷疑惡性(suspicious)、檢體不足。

結果是良性的結節一般就是定期追蹤,至於追蹤時若大小變化不大，是否要重複切片?至今尚無定論。另一方面,結果是惡性的話,無雍置疑便建議手術治療。而結果是檢體不足的話,則重複作細針穿刺切片，若再作仍是檢體不足，則視同indeterminate/suspicious的那一類去處理或直接建議手術治療。

最麻煩的是indeterminate/suspicious 這一類的判讀，因濾泡腺瘤、濾泡腺癌、Hurthle cell腫瘤、微少量colloid的增殖性甲狀腺腫(hyperplasia goiter without colloid)，有時在細胞學上無法分辨，故一般建議可以在此時安排放射碘掃描排除掉功能性結節,再建議手術切除。因有些早期的功能性結節(尤其小於2.5公分者)分泌的甲狀腺素不多，不足以壓制TSH,其在切片的細胞學表現上也類似濾泡腫瘤，而這些熱結節幾乎都是良性。

而當把惡性的結節都排除掉及開刀處理之餘，對於其他良性結節的處理，若為甲狀腺亢進的熱結節，可以放射碘治療或手術處理。至於甲狀腺功能正常或處於亞臨床亢進的熱結節，如上所述，介入性治療的時機仍爭議中。唯一要注意的是：此類結節不宜以甲狀腺素抑制療法來處理，因恐怕會演變成甲狀腺亢進。

而甲狀腺功能正常或低下的其他結節，可以不作介入性治療而只持續追蹤，另也可以在造成局部症狀時，以手術、甲狀腺素抑制療法、放射碘、局部酒精注射等方法來治療。但目前沒有什麼大規模的研究比較這些治療的預後及花費—效度的關係，連甲狀腺素抑制療法的作用目標(TSH<0.3mU/L， <0.1mUL/L)、效度、及副作用的權衡。目前也無定論(29)。

結論

甲狀腺結節的自然史顯示可變大可變小， 惡性率也極低 ，因此造成處理的爭議，最重要的是找出可能有惡性變化的結節。至於針對良性結節的各種處理的比較及評估，是我們未來可以去努力的。

十二、Subacute Thyroiditis

1.Incidence: 20-60 years, F/M: 3-6/1, more in summer

2.Etiology: viral infection

3.Clinical manifestations: neck pain, thyroid firm and tenderness (sometimes unilateral or migrated from one side to the other), systemic symptoms of inflammatory illness with or without symptoms of thyrotoxicosis

Labaratory:

Thyroid function test:4 phase:

1. acute phase (3-6 weeks, may last longer): thyrotoxicosis

fT4 ↑, T3↑, Thyroglobin↑ ,TSH↓, I131 uptake↓

2.transient asymptomatic euthyroidism

3.transient hypothyroidism(may last for several months)

4.recovery phase:

return to normal thyroid function and morphology in 4-6 months

1. ATA and AMIA: only 10-20% of patients

2. elevated ESR, often to above 100 mm/hour

Treatment: NSAID and steroid

Course: from several weeks to several months,

Prognosis:

1. relapse: 4%

2. 5-15% results in permanent hypothyroidism.

3. Graves' disease occurrence ever reported

十三、甲狀腺正能症 (Sick euthyroid illness) (Low T3 syndrome)

Clinical picture: patients with illness with abnormal thyroid function test but without typical symptoms of hypothyroidism or hyperthyroidism

Lab finding: fT3↓, rT3↑ (TSH and free T4 are usually normal)

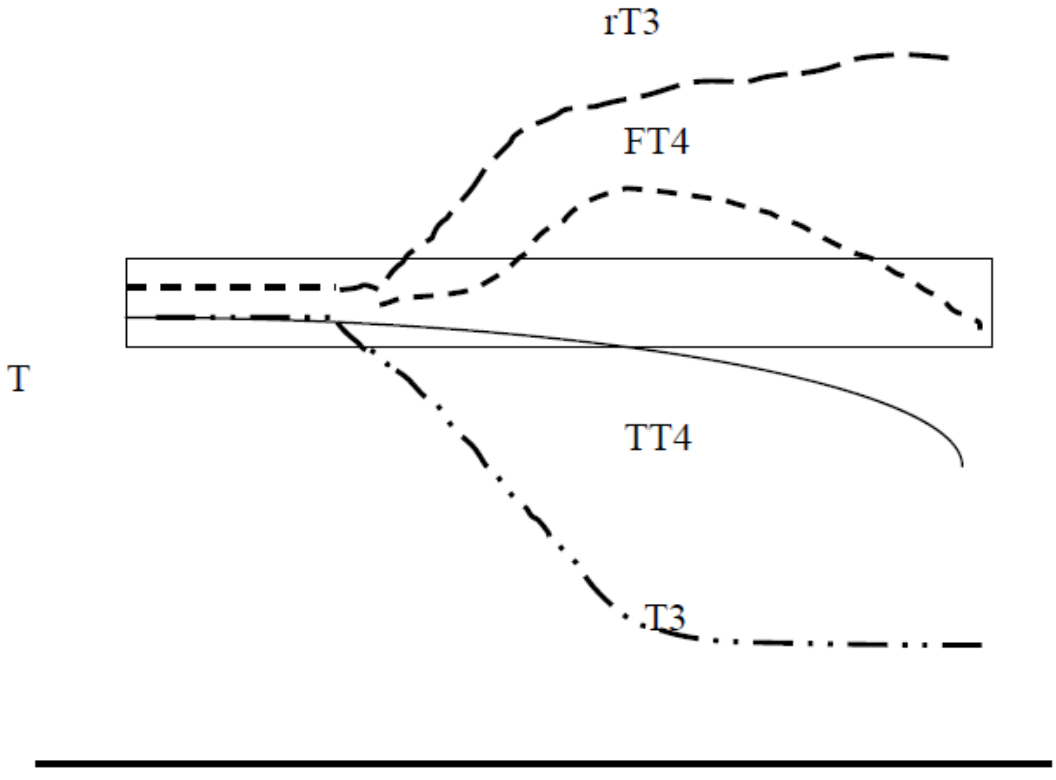
Mechanism:

1. ↓ rT3 clearance

2. str ess induced thyroid binding globulin↓

3. stress, Dopamine,dobutamine, steroid inhibit TRH secreting from hypothalamus

4. Thyroid hormone的演變:


rT3
FT4
T
TT4
T3
------SEVERITY OF ILLNESS----

十四、Adrenal Failure

1. Etiology
    a. Primary adrenal failure(Addison's disease): defiency of cortisol and aldosterone and elevated plasma adrenocorticotropic hormone(ACTH)
        - Most often due to autoimmune adrenalitis which may be associated with other endocrine deficits
        - Infections such as tuberculosis and histoplasmosis also may cause adrenal failure
        - Hemorrhagic adrenal infarction: may occur in the postoperative period, in coagulation disorders and hypercoagulable states and in sepsis. Often causes abdominal or flank pain and fever
        - Adrenoleukodystrophy: causes adrenal failure in young males
        - Drugs: ketoconazole and etomidate inhibit steroid hormone synthesis
        - AIDS: may be caused by disseminated cytomegalovirus, mycobacterial or fungal infection or adrenal lymphoma
    b. Secondary adrenal failure
        - ACTH deficiency caused by disorders of the pituitary or hypothalamus with deficiency of cortisol alone
        - Most often due to glucocorticoid therapy, ACTH suppression may persist for a year after therapy is stopped
        - Any disorder of the pituitary or hypothalamus can cause ACTH deficiency
2. Clinical findings
    a. Nonspecific and without a high index of suspicion, the diagnosis of this potentially lethal but readily treatable disease is easily missed.
    b. Symptoms include anorexia, nausea, vomiting, weight loss, weakness and fatigue. Orthostatic hypotension and hyponatremia are common.
    c. Hyperpigmentation(due to marked ACTH excess) and hyperkalemia and volume depletion(due to aldosterone deficiency) occur only in primary adrenal failure
    d. Adrenal crisis: often triggered by illness, injury or surgery. Shock may develop suddenly and is fatal unless promptly treated

3. Diagnosis

a. The short cosyntropin(cortrosyn) stimulation test: cosyntropin, 250 ug, is given IV or IM and plasma cortisol is measured 30 minutes later. The normal response is a stimulated plasma cortisol greater than 20ug/dl. This test detects primary and secondary adrenal failure except within a few weeks of onset of pituitary dysfunction(ex: shortly after pituitary surgery)

b. The distinction between primary and secondary adrenal failure

- Hyperkalemia, hyperpigmentation or other autoimmune endocrine deficits indicate primary adrenal failure
- Deficits of other pituitary hormones, symptoms of a pituitary mass(ex: headache, visual field loss) or known pituitary or hypothalamic disease indicate secondary adrenal failure.
- If the cause is unclear, the plasma ACTH level distinguishes primary adrenal failure(in which it is markedly elevated) from secondary adrenal failure.
- Most cases of primary adrenal failure are due to autoimmune adrenalitis, but other causes should be considered. Radiographic evidence of adrenal enlargement or calcification indicates that the cause is infection or hemorrhage.
- Patients with secondary adrenal failure should be tested for other pituitary hormone deficiencies and should be evaluated for a pituitary or hypothalamic tumor.

4. Therapy

a. Adrenal crisis

- If the diagnosis of adrenal failure is known: hydrocortisone, 100mg IV q8h should be given and 0.9 % saline with 5% dextrose should be infused rapidly until hypotension is corrected. The dose of hydrocortisone is decreased gradually over several days as symptoms and any precipitating illness resolve, then changed to oral maintenance therapy. Mineralocorticoid replacement is not needed until the dose of hydrocortisone is less than 100mg/day.
- If the diagnosis of adrenal failure has not been established: a single dose of dexamethasone, 10mg IV should be given and rapid infusion of 0.9% slaine with 5% dextrose should be started. A cortrosyn stimulation test should be performed. Dexamethasone

is used because it does not interfere with measurement of plasma cortisol. After the 30 minute plasma cortisol measurement, hydrocortisone, 100mg IV q8h should be given until the test result is known.

b. Maintenance therapy

- Prednisolone, 5mg PO every morning and 2.5 mg PO every evening should be started. The dose is then adjusted with the goal being the lowest dose that relieves the patients symptoms without causing osteoporosis and other signs of Cushing's symdrome. Most patients require doses between 4mgPO qd and 5mg PO bid. Concomitant therapy with rifampin, phenytoin or Phenobarbital accelerates glucocorticoid metabolism and increases the dose requirment.
- During illness, injury, or the perioperative period, the dose of prednisolone must be increased.
  (a) For minor illnesses, the patients should double the dose for 3 days. If the illness resolves, the maintenance dose is resumed. Vomiting requires immediate medical attention with IV glucocorticoid therapy and IV fluid. Patients can be given a prefilled syringe of dexamethasone, 4 mg to be self-administered IM for vomiting or severe illness if medial care is not immediately available.
  (b) For severe illness or injury, hydrocortisone 50mg IV q8h should be given with the dose tapered as severity of illness wanes. The same regimen is used in patients undergoing surgery with the first dose of hydrocortisone given preoperatively. The dose can be tapered to maintenance therapy by 2-3 dyas after uncomplicated surgery. .
- In primary adrenal failure, fludrocortisone, 0.1mg PO qd should be given along with liberal salt intake. The dose is adjusted to maintain BP(supine and standing) and serum potassium within the normal range; the usual dosage is 0.05-0.2mmg PO qd. Patients should be educated in management of their disease, including adjustment of prednisolone dose during illness. They should wear a medical identification tag or bracelet.

十五、Cushing's Syndrome

Cushing's syndrome(the clinical effects of increased glucocorticoid hormone) is most often iatrogenic due to therapy with glucocorticoid drugs.
ACTH-secreting pituitary microadenomas(Cushing's disease) account for 80% of cases of endogenous Cushing's syndrome. Adrenal tumors and ectopic ACTH secretion account for the remainder.

1. Clinical findings: include truncal obesity, rounded face, fat deposits in the supraclavicular fossae and over the posterior neck, hypertension, hirsutism amenorrhea and depression. More specific finding include thin skin, easy bruising, reddish striae, proximal muscle weakness and osteoporosis. Diabetes mellitus develops in some patients. Hyperpigmentation or hypokalemic alkalosis suggests

Cushing's syndrome due to ectopic ACTH secretion

2. Diagnosis
    c. The overnight dexamethasone suppression test(1 mg dexamethasone given PO at 11:00 PM; plasma cortisol measured at 8:00 Am the next day; normal plasma cortisol < 2ug/dl) or 24-hour urine cortisol measurement can be done as a creening test. Both tests are very sensitive and a normal value virtually excludes the diagnosis. :
    d. An abnormal screening test: indicates the need to perform a low-dose dexamethasone suppression test.
    - dexamethasone, 0.5 mg PO q6h is given for 48 yrs and urine cortisol is measured during the last 24 hrs. failure to suppress urine cortisol to less than the normal reference range is diagnostic of Cushing's syndrome. Testing should not be done during severe illness or depression which may cause false-positive results. Phenytoin therapy also causes a false-positive test by accelerating metabolism of dexamethasone. Random plasma cortisol levels are not useful for diagnosis because the wide range of normal values overlaps those of Cushing's syndrome. After the diagnosis of Cushing's syndrome is made, tests to determine the cause are best done in consultation with an endocrinologist.

Incidental Adrenal Nodules

1. Evaluation

a. In patients without a known malignancy elsewhere: the diagnostic issues are whether a syndrome of hormone excess or an adrenocortical carcinoma is present. Patients should be evaluated for hypertension, symptoms suggestive of pheochromocytoma(episodic headache, palpitation and sweating) and signs of Cushing's syndrome. Plasma potassium and dehydroepiandrosterone and 24 hrs urine catecholamines should be measured and an overnight dexamethasone suppression test should be performed.

b. In patients who have potentially respectable cancer elsewhere and in whom an adrenal metastasis must be excluded may require needle biopsy of the nodule. Pheochromocytoma should be excluded with measurement of 24-hr urine catecholamines before biopsy.

2. Management:

a. Patients with hypertension and hypokalemia should be evaluated for primary hyperaldosteronism in consultation with an endocrinologist

b. An abnormal overnight dexamethasone suppression test should be evaluated further

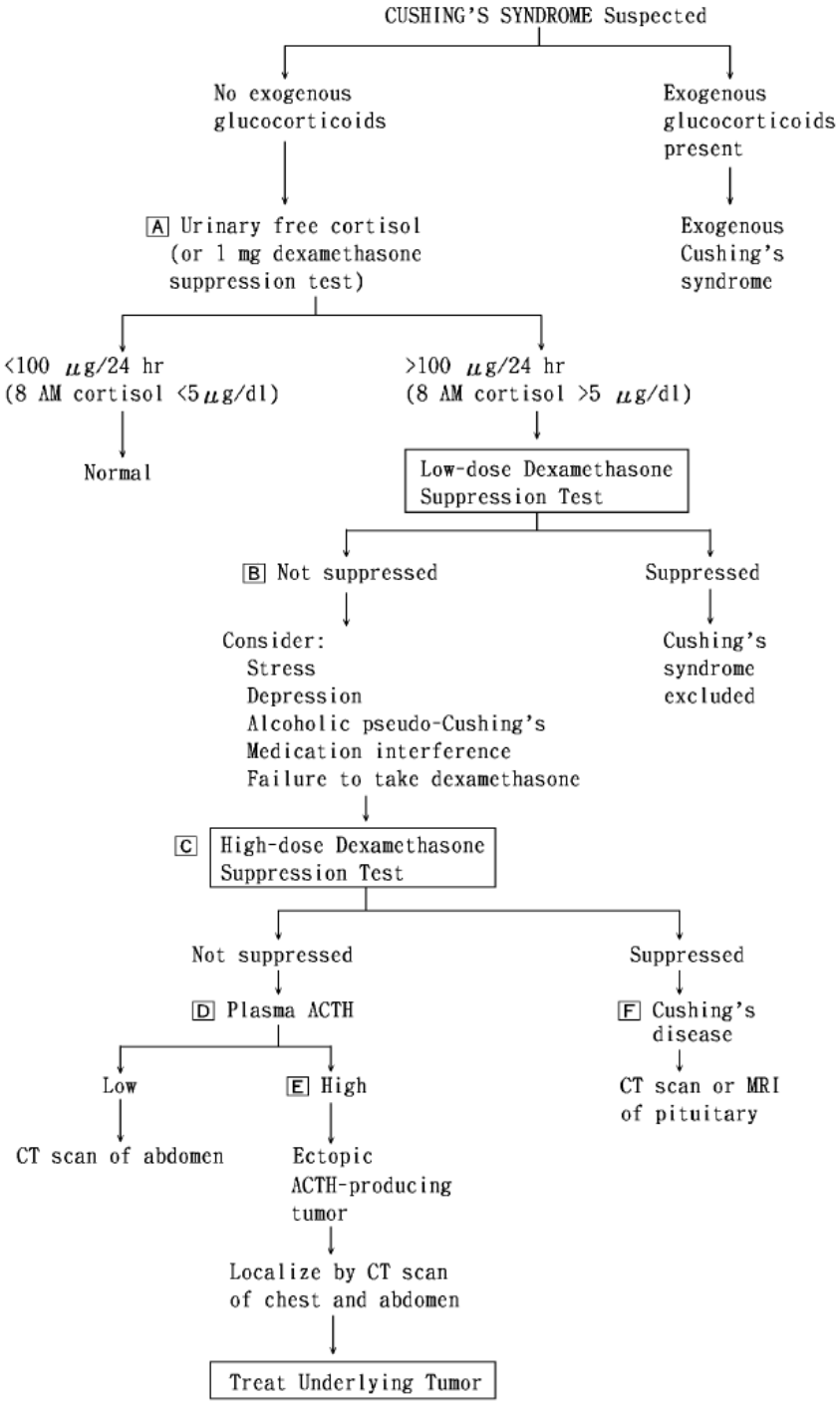
c. If there is clinical or biochemical evidence of a pheochromocytoma, the nodule should be resected after appropriate alph-adrenergic blockade with phenoxybenzamimne.

d. Elevation of plasma dehydroepiandrosterone or a large nodule suggest adrenocortical carcinoma: resecting all nodules greater than 4 cm in diameter

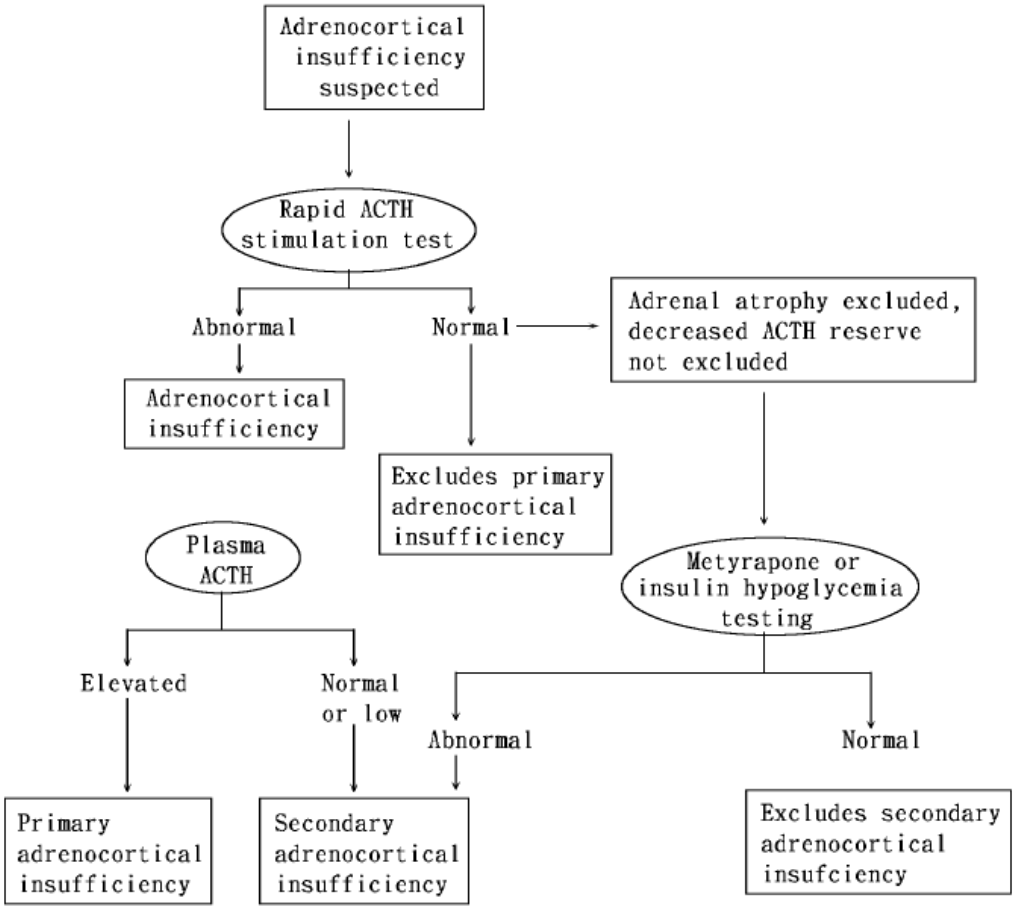
e. appropriately treats the great majority of adrenal carcinomas while minimizing the number of benign nodules removed unnecessarily. Most indicental nodules are less than 4 cm in diameter, do not produce excess hormone and do not require therapy

f. At least one repeat imaging procedure 3-6 months later is recommended to ensure that the nodule is not enlarging rapidly(which would suggest an adrenal carcinoma).

Flow chart of CUSHING'S syndrome



<Flow chart of adrenal insufficiency>



十六、高低血鈣症

Hypercalcemia

Hypercalcemia is a total serum calcium value above the normal range (8.5-10.5 mg/dl) in the presence of normal serum proteins.
A decrease or increase in serum albumin of 1 g/dl from 4 g/dl decreases or increases the serum calcium by 0.8 mg/dl.
Calcium is 50% free (ionized), 40% protein-bound (mainly to albumin), 10% complexed to phosphate, citrate, bicarbonate, sulfate and lactate.
Only elevations in the free calcium are associated with symptoms and signs.
No symptoms are usually present with mild hypercalcemia (<12 mg/dl).
Moderate (12-14 mg/dl) or severe (>14 mg/dl) hypercalcemia and rapidly developing mild hypercalcemia cause more frequent symptoms and signs.

Signs and Symptoms of Hypercalcemia

CNS: lethargy, stupor, depression, psychosis, coma.
GI: anorexia, nausea, vomiting, constipation, abdominal pain, peptic ulcer disease, acute or chronic pancreatitis.
Renal: polyuria (nephrogenic DI), polydipsia, nephrolithiasis, nephrocalcinosis, renal function impairment.
Musculoskeletal: muscle weakness, arthralgia, osteopenia, osteoporosis.
CV: hypertension, short Q-T interval of EKG, dysrhythmias, sinus arrest.
Eye: conjunctival calcification, band keratopathy.
Serum calcium is regulated by serum levels of parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (1,25(OH)2D), calcitonin, phosphate and calcium.
Serum free calcium, intact-PTH and serum phosphate should be checked first when hypercalcemia found.

Functions of PTH

Increased bone resorption of calcium and phosphate.
Increased distal renal tubular calcium reabsorption.
Decreased renal tubular phosphate reabsorption.
Increased renal production of 1,25(OH)2D.
Net effect: increased serum calcium and decreased phosphate.

Functions of 1,25(OH)2D

Increased bone resorption of calcium and phosphate.

Increased renal reabsorption of calcium and phosphate.

Increased gut absorption of calcium and phosphate.

Decreased parathyroid production of PTH.

Decreased renal production of 1,25(OH)2D.

Net effect: increased serum calcium and phosphate.

Functions of Calcitonin

Decreased bone resorption of calcium and phosphate.

Decreased renal reabsorption of calcium and phosphate.

Decreased gut absorption of phosphate.

Net effect: decreased serum calcium and phosphate.

Table 26–2. Causes of Hypercalcemia

Parathyroid-Dependent Hypercalcemia
Primary hyperparathyroidism
Tertiary hyperparathyroidism
Familial hypocalciuric hypercalcemia
Lithium-associated hypercalcemia
Parathyroid-Independent Hypercalcemia
Neoplasms
Parathyroid hormone–related protein–dependent
Other humoral syndromes
Osteolytic metastases and multiple myeloma
Excess vitamin D/1,25(OH)$_2$D
Vitamin D ingestion
1,25-Dihydroxyvitamin D intoxication
Topical vitamin D analogues
Granulomatous disease
Williams' syndrome
Thyrotoxicosis
Adrenal insufficiency
Renal failure
Acute renal failure
Chronic renal failure with aplastic bone disease
Immobilization
Jansen's disease
Drugs
Vitamin A intoxication
Milk-alkali syndrome
Thiazide diuretics
Theophylline

Primary Hyperparathyroidism

A primary abnormality of parathyroid tissue leads to excessive secretion of PTH.

The most common cause of hypercalcemia.

> 90% among hypercalcemia in outpatients.

Incidence: 4 cases per 100000 persons per year.

Peak incidence occurs in the sixth decade of life.

Two to three times more common in women.

Mostly (83%) asymptomatic with mild hypercalcemia.

Single parathyroid adenoma --- 80% Multiple parathyroid adenoma --- 5% Diffuse hyperplasia of all parathyroid glands --- 15% Parathyroid carcinoma --- 1-2%

Etiology:

Sporadic

Associated with MEN 1 or MEN 2a

Familial --- hereditary isolated primary hyperparathyroidism (autosomal dominant)

Complications of Primary Hyperparathyroidism

Bone:

Osteitis fibrosa cystica --- bone pain, marrow fibrosis, cystic lesions that may contain fibrous tissue (brown tumors), subperiosteal resorption of cortical bone, salt-and-pepper appearance of skull.

Osteoporosis --- predominant loss of cortical bone, such as mid-radius; trabecular or cancellous bone (as in vertebral bodies) is preferentially preserved.

Kidneys:

Nephrolithiasis (10-25%) --- due to hypercalciuria (urinary calcium > 4 mg/kg/day), typically occur bilaterally and usually consist of calcium oxalate, easy recurrent.

Nephrocalcinosis (rare) --- bilateral, extensive but minute calcifications that are evident on plain abdominal radiographys, usually in the renal pyramids and medullary regions. (Deposits of calcium in the epithelium of renal tubules)

Renal function impairment (35%) --- decrease in creatinine clearance.

Familial Hypocalciuric Hypercalcemia (FHH)

Autosomal dominant, also called familial benign hypercalcemia.

Mutations of the calcium-sensing receptor gene found in parathyroid glands, kidney, and other organs.

Decrease renal clearance of calcium (FEca < 1%).

Normal-to-high serum levels of PTH.

Serum Ca usually < 12 mg/dl

Mild relative hypermagnesemia.

Low serum phosphorus.

Usually asymptomatic, no associated complications and require no therapy. (exception: homozygote with severe congenital hypercalcemia, need parathyroidectomy)

Lithium-associated Hypercalcemia

Lithium increases the set-point for PTH secretion.

Lead to mild, persistent increases in serum PTH and serum Ca after several years on lithium therapy.

Usually asymptomatic mild hypercalcemia.

Substantial hypercalcemia should lead to withdrawal of lithium therapy, if possible. Blood Ca and PTH normalize within several months when lithium therapy stopped.

Hypercalcemia of Malignancy

Most malignancies produce hypercalcemia only when they are far advanced.

Patient usually die a month or two after hypercalcemia is noted.

The most common cause for hypercalcemia in hospitalized patient.

Two categories: Humoral hypercalcemia of malignancy (HHM)[80%]

Local osteolytic hypercalcemia (LOH) [20%]

Humoral Hypercalcemia of Malignancy

Mostly mediated by parathyroid hormone-related protein (PTHrP). Other humoral subtances occasionally found included transforming growth factor alpha, tumor necrosis factor, various interleukins and cytokines.

Decreased in i-PTH and P, but normal or decreased 1,25(OH)2D.

Tumors commonly found: Squamous cell carcinoma of lung, head and neck, esophagus, cervix.

Breast cancer, renal cell carcinoma, bladder cancer.

Pheochromocytoma.

Some lymphomas express 1-α hydroxylase activity, causing elevated 1,25(OH)2D level.

Local Osteolytic Hypercalcemia

Generally occurs when cancer cells are present in multiple sites throughout the skeleton.

Pathogenesis: secretion of osteoclast-stimulating factors directly onto the surface of bone. Such factors included PTHrP, lymphotoxin, interleukins, transforming growth factors, prostaglandins.

Tumor commonly found: Multiple myeloma, breast cancer with skeletal metastases, and lymphoma.

Therapy of severe hypercalcemia

(1) Volume repletion

With 0.9% normal saline.

Goal: restoration of normal GFR.

Initial infusion rate: 300-500 ml/hr, reduce after ECF volume deficit has been partially corrected.

A positive fluid balance of at least 2L should be achieved.

(2) Saline diuresis

Saline diuresis with 0.9% saline infusion (100-200 ml/hr) promotes calcium excretion after ECF volume is restored.

Serum electrolytes, calcium, and magnesium should be monitored, adequate replacement of potassium and magnesium is essential.

Thiazide diuretics must be avoided.

Furosemide, 20-40 mg iv bid-qid, adds little to the effect of saline diuresis and may prevent adequate restoration of ECF volume. It should not be given unless heart failure develops.

(3) Calcitonin

Inhibits bone resorption and increases renal calcium excretion.

Salmon calcitonin, 4-8 IU/kg IM of SC q6-12h.

Achieve a rapid response, safe in renal failure, may have analgesic effect in patients with fracture or metastatic bone disease.

Lower serum calcium 1-2 mg/dl within 2-4 hr in 60-70% of patients. Its efficacy limited to 2-3 days at most, possibly because of receptor down-regulation in target cells of bone and kidney.

Side effects: nausea, vomiting, abdominal cramps, flushing, local skin reaction and rarely, allergic reaction. (Give a skin test of 1 IU intradermally before treatment)

(4) Bisphosphonates

Inhibits osteoclastic bone resorption.

Pamidronate: 60-90 mg iv infusion 4-24 hr. 90% effective within 48 hr, peaks in nearly 5-7 days, may persist for 2-8 wk.

Zoledronate: 4 mg iv infusion over a minimum of 15 min. More potent, longer duration of response.

Etidronate: 7.5 mg/kg/day, iv infusion over 4 hr as needed each day for 5 days.

Clodronate: 300mg iv infusion for at least 2 hr each day for 5 consecutive days.

Retreatment can be conducted after recurrence of hypercalcemia.

Renal insufficiency is a relative contraindication. Increased serum creatinine (0.5 mg/dl) occurs in about 15% of patients. Reduced doses and maximal infusion time in renal failure. (Sr Cr > 2.5 mg/dl)

Side effects: transient fever (20%), myalgia (20%), local pain or swelling at infusion site, transient lymphopenia, mild hypophosphatemia or hypomagnesemia.

(5) Glucocorticoids

Mechanism: no clear answer. Inhibit synthesis and action of 1,25(OH)2D, inhibiting cytokine release, direct cytolytic effects on some tumor cells.

May be effective to hypercalcemia caused by multiple myeloma, lymphoma, granulomatous disease such as sarcoidosis, Vit A or Vit D intoxication.

Prednisone: 20-50 mg bid or its equivalent.

Serum Ca may take 5-10 days to fall.

(6) Gallium nitrate

200mg/m2 BSA/ day iv infuse over 24 hr each day for 5 days.

Decrease bone resorption.

Normalize serum calcium within 5-7 days.

Side effects: significant nephrotoxicity, hypophosphatemia, anemia.

No longer use now. (not available in Taiwan)

(7) Plicamycin (Mithramycin)

Decrease bone resorption.

15-25 ug/kg/day, iv infuse over 4 hr as needed every 2-3 days.

Significant bone marrow and hepatic toxicity.

No longer use now. (not available in Taiwan)

(8) Phosphate

Mechanism: impairs osteoclastic bone resorption and renal synthesis of 1,25(OH)2D, increase calcium x phosphate product and precipitates with calcium in bone, blood vessels and soft tissue. Binding intraluminal calcium and impairing its absorption.

IV phosphate should never be used --- may cause life-threatening hypocalcemia or hypotension.

Oral phosphate: 0.5-1.0 g po tid. Adjunct to other therapy, avoid if impaired renal function or serum P > 3.5 mg/dl, or product of serum calcium x phosphorus > 60.

Side effects: nausea, abdominal cramps, diarrhea, soft tissue calcification.

(9) Dialysis

Peritoneal or hemodialysis.

Very effective.

Particularly helpful for patients with CHF or renal insufficiency.

Treatment for Primary Hyperparathyroidism

The definitive treatment of primary hyperparathyroidism is parathyroidectomy.

There is no definitive medical therapy for hyperparathyroidism.

In postmenopausal women, estrogen replacement therapy in high doses will produce an average decrease of 0.5-1.0 mg/dl in the serum Ca and increase in BMD. Serum PTH remains elevated, serum 1,25(OH)2D increases. (Some risk of CV disease exist with high dose estrogen)

Raloxifene (selective estrogen receptor modulators) --- beneficial effect has not yet been shown.

Bisphosphonates --- increase vertebral bone density, stimulation of PTH secreation, no change of serum Ca, aggravates hypophosphatemia and augment renal 1,25(OH)2D synthesis.

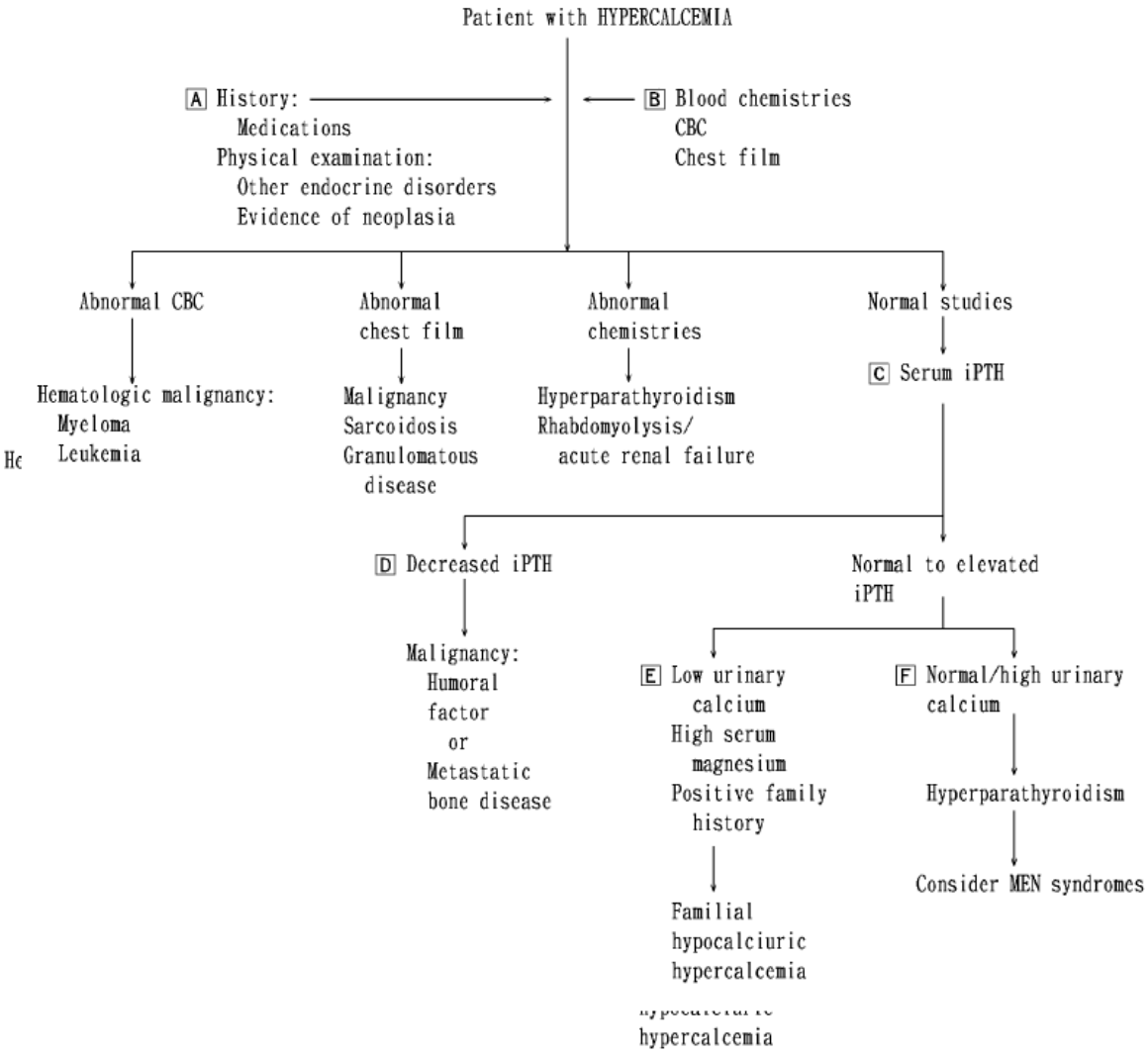
Oral phosphate --- inhibit synthesis of 1,25(OH)2D and osteoclastic bone resorption, but increase serum PTH, long term effect on bone unknown.

Calcimimetic drug: Cinacalcet --- bind to calcium sensor/receptor on parathyroid cells and alter their sensitivity to calcium, decrease PTH, normalization of serum Ca. BMD: unchange.

Criteria for parathyroid surgery in patients with asymptomatic primary hyperparathyrodism (NIH Guideline 2002)

1) Serum Ca 1.0 mg/dl above upper limit of normal
2) 24 hrs urinary calcium excretion > 400mg
3) Reduction in Ccr > 30%
4) Bone mineral density T score < -2.5 at any site
5) Age < 50 years old

Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible.



Hypocalcemia

Table 8–6. Causes of hypocalcemia.

- **Hypoparathyroidism**
  - Surgical
  - Idiopathic
  - Neonatal
  - Familial
  - Deposition of metals (iron, copper, aluminum)
  - Postradiation
  - Infiltrative
  - Functional (in hypomagnesemia)
- **Resistance to PTH action**
  - Pseudohypoparathyroidism
  - Renal insufficiency
  - Medications that block osteoclastic bone resorption
    - Plicamycin
    - Calcitonin
    - Bisphosphonates
- **Failure to produce $1,25(OH)_2D$ normally**
  - Vitamin D deficiency
  - Hereditary vitamin D-dependent rickets, type 1 (renal 25-OH-vitamin D 1α-hydroxylase deficiency)
- **Resistance to $1,25(OH)_2D$ action**
  - Hereditary vitamin D-dependent rickets, type 2 (defective VDR)
- **Acute complexation or deposition of calcium**
  - Acute hyperphosphatemia
    - Crush injury with myonecrosis
    - Rapid tumor lysis
    - Parenteral phosphate administration
    - Excessive enteral phosphate
      - Oral (phosphate-containing antacids)
      - Phosphate-containing enemas
  - Acute pancreatitis
  - Citrated blood transfusion
  - Rapid, excessive skeletal mineralization
    - Hungry bones syndrome
    - Osteoblastic metastasis
    - Vitamin D therapy for vitamin D deficiency

Clinical manifestations

Chronic hypocalcemia may be asymptomatic.

Alkalosis augments calcium binding to albumin → free Ca decrease → increases the severity of symptoms.

Paresthesias and tetany, carpopedal spasms.

Trousseau's sign --- development of carpal spasm when a BP cuff is inflated above SBP for 3 minutes.

Chvostek's sign --- twitching of the facial muscles when the facial nerve is tapped anterior to the ear.

Severe hypocalcemia may cause lethargy, confusion, laryngospasm, seizures, or heart failure.

EKG may show a prolonged QT interval.

Chronic hypocalcemia may cause cataracts and calcification of the basal ganglia.

Laboratory studies

Serum P level is elevated in hypocalcemia resulting from most causes, though in Vit D deficiency, it is usually low.

Serum PTH is elevated in disorders other than hypoparathyroidism and magnesium deficiency.

Acute management of symptomatic hypocalcemia

2 g calcium gluconate (180 mg elemental calcium or 20 ml 10% calcium gluconate) iv over 10 minutes, followed by infusion of 6 g calcium gluconate in 500 ml D5W over 4-6 hours. (10 ml 10% calcium gluconate = 1 g = 90 mg of elemental calcium)

Serum Ca should be measured q4-6h, the target is to keep serum Ca between 8 and 9 mg/dl.

Parenteral calcium is only necessary if the patient is symptomatic or has a prolonged QT interval.

Oral calcium and a rapidly acting preparation of Vit D should be started.

Hypomagnesemia, if present, must be treated to correct hypocalcemia.

Long-term management of hypocalcemia

Hypoparathyroidism and pseudohypoparathyroidism requires calcium and Vit D supplements.

The target is to maintain serum Ca levels at slightly below the normal range (8.0–8.5 mg/dl), which usually prevents manifestations of hypocalcemia and minimizes hypercalciuria.

If urine Ca > 250 mg/24 hrs, the dose of Vit D should be reduced. If hypercalciuria develops at serum Ca levels of < 8.5 mg/dl, hydrochlorothiazide (50mg po qd) can be used to reduce urinary calcium excretion.

Oral calcium

Calcium carbonate --- initial dosage is 1–2 g elemental calcium po tid during the transition from iv to oral therapy. For long-term therapy, the typical dosage is 0.5–1.0 g po tid with meals. Side effect: dyspepsia and constipation.

Vit D

Dietary deficiency can be corrected by 400–1000 IU/day, but treatment of other hypocalcemic disorders requires much larger doses.

In patients with severe hyperphosphatemia, serum P should be lowered to < 6.5 mg/dl with oral phophate binders before Vit D is started.

Calcitriol (0.25 or 0.5 μg/cap) has a rapid onset of action. The initial dosage is 0.25 μg po qd, and most patients are maintained on 0.5–2.0 μg po qd. The dose can be increased at 2–4 week intervals.

Vitamin D (50000 IU or 1.25 mg/cap) requires weeks to achieve full effect. The initial dosage is 50000 IU po qd, and usual maintenance dosages are 25000–100000 IU po qd. The dose can be increased at 4–6 week intervals.

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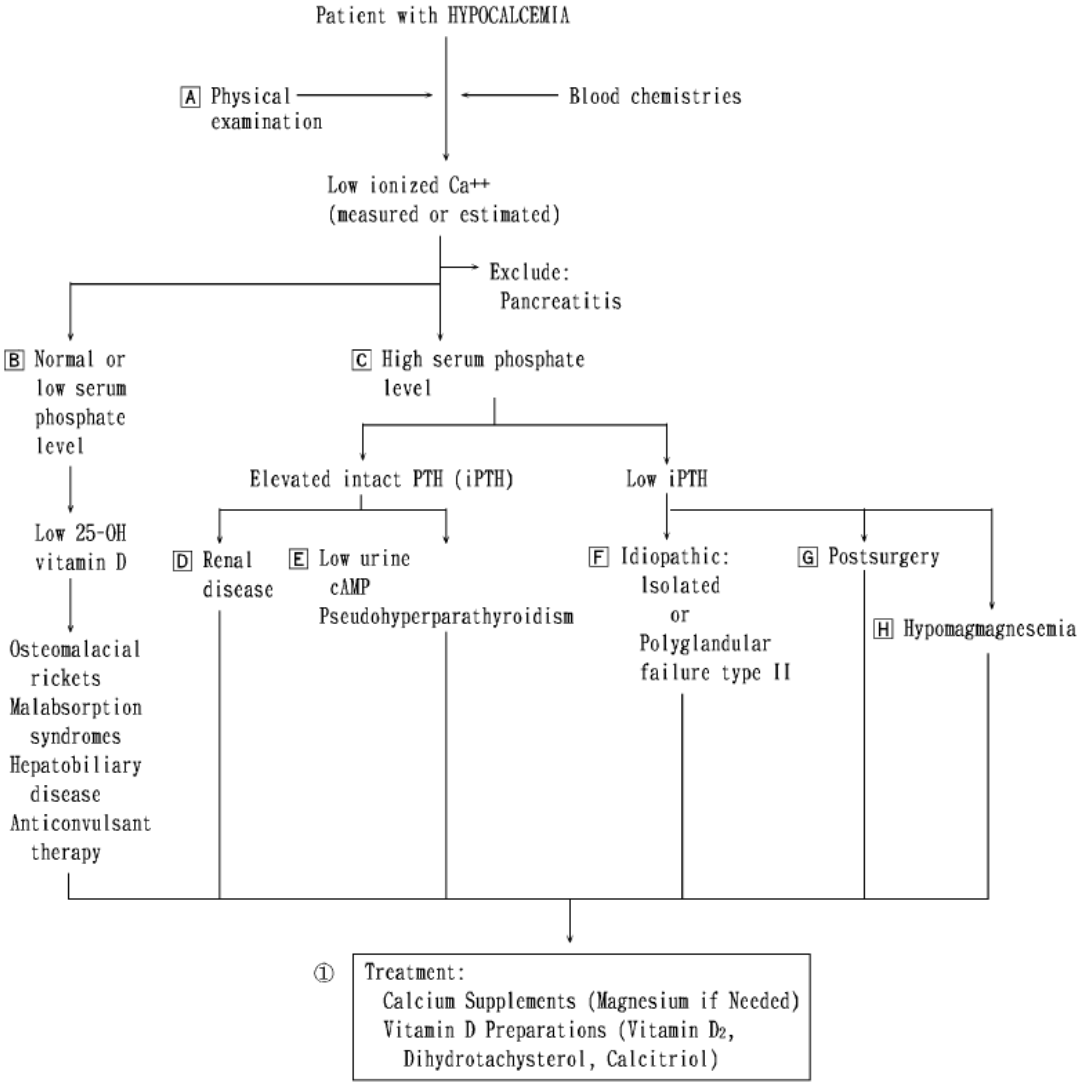
Patient with HYPOCALCEMIA
A Physical examination
Blood chemistries
Low ionized Ca++
(measured or estimated)
Exclude:
Pancreatitis
B Normal or low serum phosphate level
C High serum phosphate level
Low 25-OH vitamin D
Elevated intact PTH (iPTH)
Low iPTH
D Renal disease
E Low urine cAMP
Pseudohyperparathyroidism
F Idiopathic: Isolated or Polyglandular failure type II
G Postsurgery
H Hypomagmagnesemia
Osteomalacial rickets
Malabsorption syndromes
Hepatobiliary disease
Anticonvulsant therapy
①
Treatment:
Calcium Supplements (Magnesium if Needed)
Vitamin D Preparations (Vitamin D2, Dihydrotachysterol, Calcitriol)

Metabolic Bone Disease

Osteomalacia

Defective mineralization of osteoid.

Causes of osteomalacia:

1. Vitamin D deficiency
2. Malabsorption of Vit D and calcium due to intestinal, hepatic, or biliary disease
3. Disorders of Vit D metabolism (eg. renal disease, vitamin D-dependent rickets)
4. Vit D resistance
5. Chronic hypophosphatemia
6. Renal tubular acidosis
7. Hypophosphatasia
8. Therapy with anticonvulsants, fluoride, etidronate, or aluminum compounds.

Clinical manifestations:

Diffuse skeletal pain, proximal muscle weakness, saddling gait, and propensity to fractures.

Serum alkaline phosphatase is elevated, serum phosphorus, calcium, or both may be decreased.

Radiographic findings: osteopenia, radiolucent bands perpendicular to bone surfaces (pseudofractures or Looser's zones).

Bone biopsy: increased thickness of osteoid seams and decreased mineralization rate.

Treatment:

Dietary Vit D deficiency can initially be treated with vitamin D 50000 IU po weekly for several weeks, followed by long-term therapy with 400–1000 IU/day.

Malabsorption of vitamin D may require therapy with high doses, ranging from 50000 IU po weekly to 50000 IU po qd. Calcitriol, 0.5–2.0 μg po qd, can also be used.

Calcium supplements, 1 g po qd-tid, may also be required.

Serum 25(OH)D, serum Ca, and 24-hrs urine calcium should be monitored every 3–6 months to avoid hypercalcemia or hypercalciuria.

Paget's disease of bone

A focal skeletal disorder characterized by rapid, disorganized bone remodeling.

Usually occurs after age 40 and most often affects the pelvis, femur, spine, and skull.

Clinical manifestations:

Most patients are asymptomatic.

Bone pain and deformity, degenerative arthritis, pathologic fractures, neurologic deficits due to nerve root or cranial nerve compression(including deafness), and rarely, high output heart failure and osteogenic sarcoma.

Diagnosis:

The radiographic appearance is usually diagnostic, and biopsy is rarely necessary. Serum alkaline phosphatase is elevated. Serum and urine calcium are usually normal.

Indications for therapy:

1. bone pain
2. nerve compression syndromes
3. pathologic fracture
4. elective skeletal surgery
5. progressive skeletal deformity
6. immobilization hypercalcemia
7. hypercalciuria with nephrolithiasis
8. high-output heart failure
9. asymptomatic involvement of weight-bearing bones or the skull

Treatment:

Bisphosphonates inhibit excessive bone resorption, relieve symptoms, and restore serum alkaline phosphatase and bone deposition to normal in most patients.

Alendronate 40 mg/day for 6 months, or risedronate 30 mg/day for 2–3 months. The effectiveness of therapy is monitored by measuring serum alkaline phosphatase every 3 months.

Reference:

1. Green GB, Harris IS, Lin GA, Moylan KC. The Washington Manual of Medical Therapeutics. 31st Edition 2004; pg: 56-62.

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十七、Anterior Pituitary Gland Dysfunction

The anterior pituitary gland secretes prolactin, growth hormone, corticotropine (ACTH), thyrotropin (TSH), luteinizing hormone and follicle-stimulating hormone. Anterior pituitary function is regulated by hypothalamic hormones that reach the pituitary via portal veins in the pituitary stalk. The predominant effect of hypothalamic regulation is to stimulate secretion of pituitary hormones, except for prolactin, which is inhibited by hypothalamic dopamine production. Secretion of trophic hormones is also regulated by negative feedback by their target gland hormone, and the normal pituitary response to target hormone deficiency is increased secretion of the appropriate trophic hormone.

Ⅰ.Anterior pituitary dysfunction can be caused by disorders of either the pituitary or hypothalamus.

A. Pituitary adenomas are the most common pituitary disorder. They are classified by size and function. Microadenomas are less than 10mm in diameter and cause clinical manifestations only if they produce excess hormone. Macroadenomas are greater than 10mm in diameter and may produce any combination of pituitary hormone excess, hypopituitarism, and mass effects. Secretory adenomas produce prolactin, growth hormone, or ACTH. Nonsecretory macroadenomas may cause hypopituitarism or mass effects. Nonsecretory microadenomas are common incidental radiographic findings, seen in approximately 10% of the normal population, and do not require therapy.

B. Other pituitary or hypothalamic disorders, such as head trauma, pituitary surgery or radiation, and postpartum pituitary infarction (Sheehan's syndrome) may cause hypopituitarism. Other tumors of the pituitary or hypothalamus (e.g., craniopharyngioma, metastases), infiltrative disorders (e.g., sarcoidosis, hemochromatosis,and histiocytosis X), and infections (e.g., tuberculosis, syphilis, and mycotic infection) may cause hypopituitarism or mass effects.

Ⅱ. Clinical findings. Pituitary and hypothalamic disorders may present in several ways.

A. In hypopituitarism (deficiency of one or more pituitary hormones), gonadotropin deficiency is most common, causing amenorrhea in women and androgen deficiency in men. Secondary hypothyroidism or adrenal failure rarely occurs alone.

B. Hormone excess is most commonly hyperprolactinemia, which can be due to a secretory adenoma or to nonsecretory lesions that damage the hypothalamus or pituitary stalk, resulting in loss of inhibition by hypothalamic dopamine.

C. Mass effects due to pressure on adjacent structures, such as the optic chiasm, include headaches and loss of visual fields or acuity.

D. Asymptomatic pituitary adenomas

1. If a microadenoma is found on imaging done for another purpose, the patient should be evaluated for clinical evidence of hyperprolactinemia, Cushing's disease, or acromegaly. Plasma prolactin should be measured, and the tests for acromegaly and Cushing's syndrome should be performed if symptoms or signs of these disorders are evident. If no pituitary hormone excess exists, therapy is not required.

2. Incidental discovery of a macroadenoma is unusual. Patients should be evaluated for hormone excess and hypopituitarism. Most macroadenomas should be treated because they are likely to grow further.

Ⅲ. Diagnosis of hypopituitarism. Hypopituitarism may be suspected in the presence of clinical signs of target hormone deficiency (e.g., hypothyroidism) or pituitary mass effects.

A. Symptoms: impairment of GH secretion causes decreased growth in children but may be occult in adult patients. GH deficiency is associated with a decreased sense of well-being and a lower health-related quality of life. Hypogonadism, manifested by amenorrhea in women and decreased libido or erectile dysfunction in men, may antedate the clinical appearance of a hypothalamic-pituitary lesion.

Hypothyroidism caused by TSH deficiency generally simulates the clinical changes observed in primary thyroid failure: however, it is usually less severe, and goiter is absent.

ACTH deficiency causes adrenocortical insufficiency, and its clinical

features resemble those of primary adrenal failure. Weakness, nausea, vomiting, weight loss, fever, and hypotension may occurred.
The only symptom of PRL deficiency is failure of postpartum lactation.

B. Signs: Patient with pituitary failure are usually slightly overweight. The skin is fine, pale, and smooth, with fine wrinkling of face. Body and pubic hair may be deficient or absent, and atrophy of genitalia may occurred. Neuro-ophthalmologic abnormalities depend on the presence of a large intrasellar or parasellar lesion.

C. Laboratory evaluation for hypopituitarism begins with evaluation of target hormone function, including plasma free T4 and Cortrosyn stimulation test. In men, plasma testosterone should be measured. The best evaluation of gonadal function in women is the menstrual history.

D. If a target hormone is deficient, its trophic hormone is measured to determine whether target gland dysfunction is secondary to hypopituitarism. In hypopituitarism, trophic hormone levels are not elevated and are usually within (not below) the reference range. Thus, pituitary trophic hormone levels can be interpreted only with knowledge of target hormone levels, and measurement of trophic hormone levels alone is useless in the diagnosis of hypopituitarism.

Ⅳ. Anatomic evaluation of the pituitary gland and hypothalamus is done best by MRI. However, hyperprolactinemia and Cushing' s disease may be caused by microadenomas that are too small to be seen with current techniques. Visual acuity and visual fields should be tested when imaging suggests compression of the optic chiasm.

Ⅴ. Treatment of hypopituitarism. Deficient target hormones should be replaced. Treatment of secondary hypothyroidism should be monitored by measurement of plasma free T4. Infertility due to gonadotropin deficiency may be correctable, and patients who wish to conceive should be referred to an endocrinologist. Treatment of growth hormone deficiency in adults has been advocated by some, but the benefits and cost-effectiveness of this therapy are not established. Treatment of pituitary macroadenomas generally requires transsphenoidal surgical resection, except for prolactin-secreting tumors.

Ⅵ. Hyperprolactinemia. In women, the most common causes of pathologic hyperprolactinemia are prolactin-secreting pituitary microadenomas and idiopathic hyperprolactinemia. In men, the most common cause is a

prolacting-secreting macroadenoma. Hypothalamic or pituitary lesions that cause deficiency of other pituitary hormones often cause hyperprolactinemia. Medications are an important cause in men and in women (e.g., Dopamine antagonists, verapamil, cimetidine, some antidepressants).

A. Clinical findings. In women, hyperprolactinemia causes amenorrhea or irregular menses and infertility. Only approximately one-half of these women have galactorrhea. In men, hyperprolactinemia causes androgen deficiency and infertility but not gynecomastia; mass effects and hypopituitarism are common.

B. Diagnosis. Plasma prolactin should be measured in women with amenorrhea, whether or not galactorrhea is present. Mild elevations should be confirmed by repeat measurements. The history should include medications and symptoms of pituitary mass effects or hypothyroidism. Laboratory evaluation should include plasma TSH and a pregnancy test in women. Prolactin levels of greater than 200 ng/ml occur only in prolactinomas, and levels between 100 and 200 ng/ml strongly suggest this diagnosis. Levels lower than 100 ng/ml may be due to any cause except prolactin-secreting macroadenoma. Testing for hypopituitarism is needed only in patients with a macroadenoma or hypothalamic lesion. Pituitary imaging should be performed in most cases, as large nonfunctional pituitary or hypothalamic tumors may present with hyperprolactinemia.

C. Therapy

1. Microadenomas and idiopathic hyperprolactinemia. Most patients are treated because of infertility or to prevent estrogen deficiency and osteoporosis. In most patients, hyperprolactinemia does not worsen, and prolactin levels sometimes return to normal. Enlargement of microadenomas is rare.

   a. The dopamine agonists bromocriptine and cabergoline suppress plasma prolactin and restore normal menses and fertility in most women. Initial dosages are bromocriptine, 1.25-2.5mg PO qhs with a snack, or cabergoline, 0.25mg twice a week. Plasma prolactin levels are initially obtained at 2- to 4-week intervals, and doses are adjusted until the lowest dose required to maintain prolactin in the normal range is reached. Maximally effective doses are 2.5mg bromocriptine tid and 1.5mg cabergoline twice a week. Side effects include nausea and orthostatic hypotension, which can be minimized by increasing the dose gradually, and usually resolve

with continued therapy. Side effects are less severe with cabergoline.

b. Women who want to become pregnant should be managed in consultation with an endocrinologist.

c. Women who do not want to become pregnant should be followed with clinical evaluation and plasma prolactin levels every 6-12 months. Every 2 years, plasma prolactin should be measured after bromocriptine has been withdrawn for several weeks, to determine whether the drug is still needed. Follow-up imaging studies are not warranted unless prolactin levels increase substantiolly.

d. Transsphenoidal resction of prolactin-secreting microadenomas is used only in the rare patient who does not respond to or cannot tolerate dopamine agonists. Prolactin levels usually return to normal, but up to one-half of patients experience relapse.

e. Transsphenoidal surgery is indicated to relieve mass effects and to prevent further tumor growth if the tumor dose not shrink or if visual field abnormalities persist during dopamine agonist therapy. However, the likelihood of surgical cure of hyperprolactinemia due to a macroadenoma is low, and most patients require further therapy with a dopamine agonist.

f. Women with prolactin-secreting macroadenomas should not become pregnant unless the tumor has been resected surgically, as the risk of symptomatic enlargement during pregnancy is 15-35%. Barrier contraception is essential during dopamine agonist treatment.

2. Prolactin-secreting macroadenomas should be treated with a dopamine agonist, which usually suppresses prolactin levels to normal, reduces tumor size, and improves or corrects abnormal visual fields in 90% of causes. If mass effects are present, the dose should be increased to maximally effective levels over a period of several weeks. Visual field tests, if initially abnormal, should be repeated 4-6 weeks after therapy is started. Pituitary imaging should be repeated 3-6 months after initiation of therapy. If tumor shrinkage and correction of visual abnormalities are satisfactory, therapy can be continued indefinitely, with periodic monitoring of plasma prolactin levels. The full effect on tumor size may take more than 6 months. Further pituitary imaging is probably not warranted unless prolactin levels rise despite therapy.

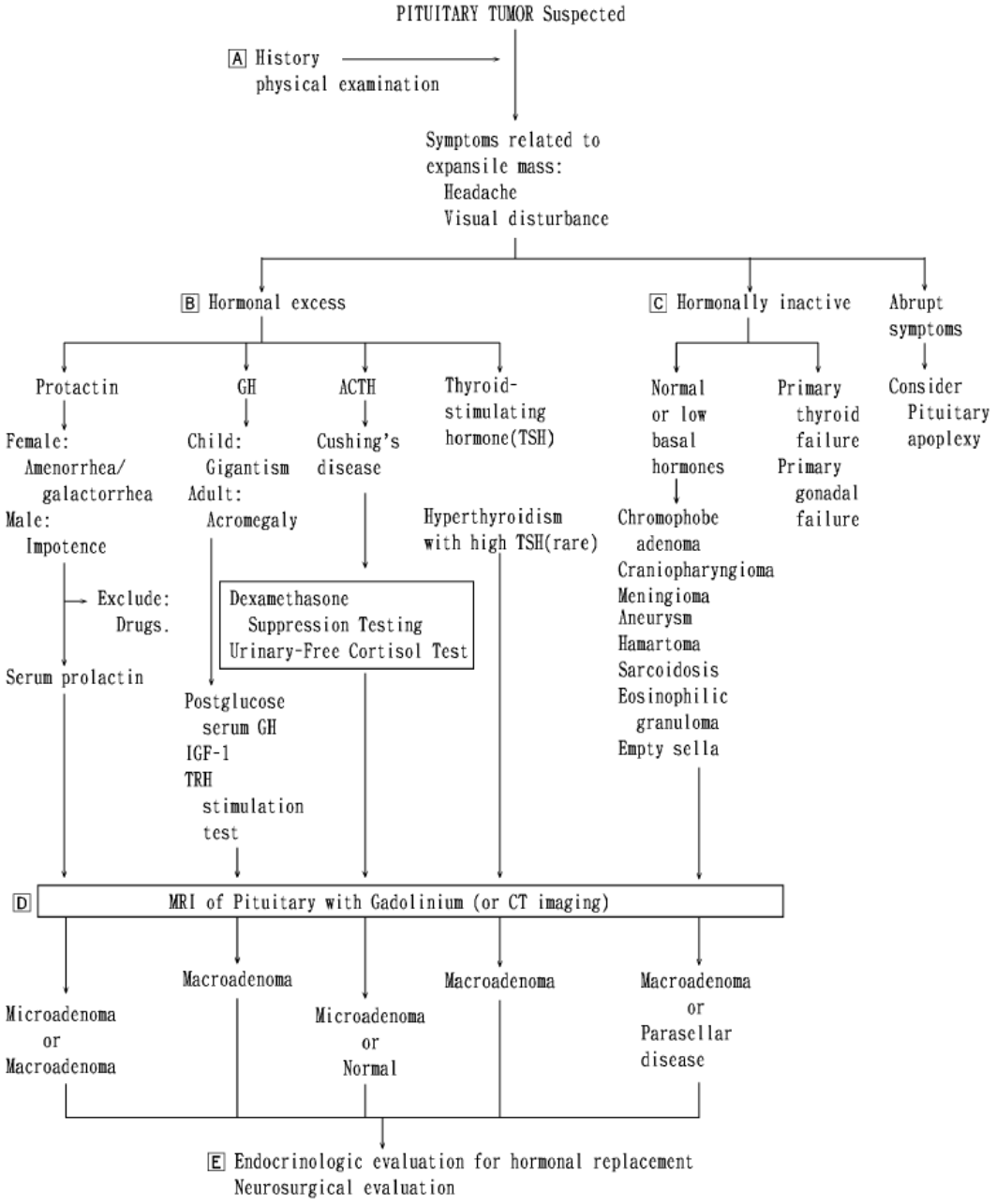
Ⅶ. Acromegaly is the syndrome caused by growth hormone excess in adults and is due to a growth hormone-secreting pituitary adenoma in the vast majority of cases. Clinical findings include thickened skin and enlargement of hands, feet, jaw, and forehead. Arthritis or carpal tunnel syndrome may develop, and the pituitary adenoma may cause headaches and vision loss. Mortality from cardiovascular disease is increased.

A. Diagnosis. Plasma insulin-like growth factor Ⅰ, which mediates most effects of growth hormone, is the best diagnostic test. Marked elevations establish the diagnosis. If IGF-1 levels are only moderately elevated, the diagnosis can be confirmed by giving 75 mg glucose orally and measuring serum growth hormone q30min for 2 hours. Failure to suppress growth hormone to less than 2 ng/ml confirms the diagnosis of acromegaly. Once the diagnosis is made, the pituitary should be imaged.

B. Therapy. The treatment of choice is transsphenoidal resection of the pituitary adenoma. Most patients have macroadenomas, and complete tumor resection with cure of acromegaly often is impossible. If IGF-1 levels remain elevated after surgery should currently be treated with sustained-release form of somatostatin analog. Radiotherapy should be reserved for those patients with inadequate responses to surgery and medical therapy.

1. The somatostatin analong octreotide in depot form can be used to suppress growth hormone secretion. A dose of 10-30 mg IM monthly suppresses IGF-1 to normal in most patients. Side effects include cholelithiasis, diarrhea, and mild abdominal discomfort.
2. Pegvisomant is a growth hormone antagonist that lowers IGF-1 to normal in almost all patients. The dosage is 10-30 mg SC qd. Few side effects have been reported, but patients should be monitored for pituitary adenoma enlargement and transaminase elevation..
3. Current guidelines for remission are a fasting GH of 2 ng/ml or less and a glucose-suppressed GH of 2 ng/ml or less accompanied by a normal level of IGF-I.

腦下垂體腫瘤


PITUITARY TUMOR Suspected
A History physical examination
Symptoms related to expansile mass:
Headache
Visual disturbance
B Hormonal excess
C Hormonally inactive
Abrupt symptoms
Protactin
GH
ACTH
Thyroid-stimulating hormone(TSH)
Normal or low basal hormones
Primary thyroid failure
Primary gonadal failure
Consider Pituitary apoplexy
Female: Amenorrhea/ galactorrhea
Male: Impotence
Child: Gigantism
Adult: Acromegaly
Cushing's disease
Hyperthyroidism with high TSH(rare)
Chromophobe adenoma
Craniopharyngioma
Meningioma
Aneurysm
Hamartoma
Sarcoidosis
Eosinophilic granuloma
Empty sella
Exclude: Drugs.
Dexamethasone Suppression Testing
Urinary-Free Cortisol Test
Serum prolactin
Postglucose serum GH
IGF-1
TRH stimulation test
D MRI of Pituitary with Gadolinium (or CT imaging)
Microadenoma or Macroadenoma
Macroadenoma
Microadenoma or Normal
Macroadenoma
Macroadenoma or Parasellar disease
E Endocrinologic evaluation for hormonal replacement
Neurosurgical evaluation

肆、動態內分泌功能試驗及週邊血管、甲狀腺超音波檢查

(1) Oral glucose tolerance test

*Diagnosis of asymptomatic diabetes melitus in the absence of fasting hyperglycemia in 2 hour test

*To rule in or rule out postprandial hypoglycemia (reactive functional, or diabetes mellitus with reactive hypoglycemia, or alimentary hyperin-sulinism-all five hour tests).

PROCEDURE

*At least 250 grams carbohydrate should be eaten daily three days before OGTT

*The patient is to eat nothing from 10 p.m. the evening before until after the test is finished. The glucose tolerance test is performed in the morning.

*Patient drinks glucose solution pre-packed glucose powder 75 gm/hag in 300 cc water over a period of up to 10 minutes.

*Draw venous blood specimens every 1/2 hour for two hours if test to be performed is for diagnosis of diabetes. If test to be performed is for diagnosis of hypoglycemia, specimens should be obtained every 1/2 hour diagnosis of hypoglycemia, specimens should be obtained every 1/2 hour for five hours.

Interpretation

	Class	Fasting	Midtest	2-hour
WHO				
	Normal	＜100	—	and ＜126
	IGT	＜126	—	and 126-199
	Diabetes	≧126	—	or ≧200

Diagnostic criteria during pregnancy. Gestational diabetes mellitus if two or more of the values are met or exceeded (criteria of J.B. O'Sullivan)(100gram glucose)

	Fasting	1-h	2-h	3-h	
Plasma glucose	95	180	155	140	mg/dl

(2) Oral glucose tolerance test-growth hormone

* The administratio of oral glucose tolerance test to normal subjects usually results in depression of plasma GH levels. In active acromegalic patients it fails to show such suppression and may demonstrate a rise in GH instead.

Procedure

* Fast overnight is necessary

*Glucose powder 75 g/pack dissolved in 300 ml of water

*Draw blood as -30 min sampling for GH and blood glucose

*Have the patient drink the glucose solution over a period of up to 10 minutes.

*Blood sampling at 30, 60, 90, 120, and 180 minutes for GH and blood glucose

Interpretation

In normal subjects,GH falls to lower than 2 ng/ml or undetectable levels within 30 minutes to 2 hours, though a later rebound of GH levels is common. Acromegaly will demonstrate either no suppression, partial suppression or paradoxical rise (often greater than 5-10 ng/ml). In addition, BS levels show impaired glucose tolerance or
Diabetes range.

(3) TRH stimulation test

*To differentiate hyperthyroxinemia with nonsuppressed TSH due to
TSH-secreting pituitary adenoma or thyroid hormone resistance syndrome

*In patients who appear euthyroid (by clinical data and results of other laboratory tests), but who have eye changes that suggest Gravesophthalmopathy, the TRH test gives a sensitive index of minor aberrations in the pituitary-thyroid axis

Procedure

*TRH 500 μ g by IV injection and draw TSH at 0,30 and 60 minutes following TRH

Interpretation

*TSH rises with an average peak at 20-40minutes(generally an increment of 15 μ U/ml for adults) and then fall at 60 minutes(less than 2/3 of peak levels). In men over 40, the response is smaller and increment of 2 μ U/ml is considered normal.

*Euthyroid Graves' disease demonstrate blunted response or absent response to TRH .

*TSH secreting adenoma shows no TSH response following TRH injection, while
TSH levels increaseas usual in thyroid hormone resistance syndrome

(4) LH-RH stimulation test

Procedure

*Studies in females should preferrably by done in the early follicular phase of menstrual cycle (days 1-7)

*at least two blood samples should be obtained 15 minutesprior to and immediately before GnRH administration. The average of the two samples serves as the baseline LH and FSH.

*GnRH 0.1 mg is given as a bolus by rapid IV injection after obtaining the -15 and 0 minutes samples. Draw blood samples for LH and FSH at 15, 30, 45, 60, 90, and 120 minutes after GnRH administration.

Interpretation

The LH response to GnRH is usually more pronounced and is seen earlier than the FSH response. In normal adults, LH peaks are generally found at 15 to 45 minutes, whereas FSH peaks may occur later in some patients. In adults, LH levels will at least double following GnRH administration. The FSH rise is usually less than twofolds and it is not unusual to see little change in FSH levels even in normal adults. Decreased response of plasma gonadotropins may indicate either pituitary disease or prolonged endogenous deficiency of GnRH.

(5) Cortrosyn stimulation test

* To determine the functional capacity of the adrenal cortex by measuring the change in plasma cortisol levels during the administration of ACTH.

*If the patient has suspected symptoms of acute adrenocortical insufficiency, Treatment with dexamethasone 0.25mg administered orally every 8 hours beginning 24 hours prior to the test and continuing for the duration of the test will not interfere with his response of ACTH. The patient should be fed as usual on the day of the ACTH test.

Procedure

*Cortrosyn depot 1mg intramuscularly at time 0 minutes.

*Collect blood for determination of cortisol levels before and at 60 minutes after the injection.

*Follow the serum cortisol level at 24th hour if seconadry adrenal insufficiency suspected

Interpretation

*Normally, serum cortisol rises to a level greater than 20ug/dl at 60 minutes. Primary adrenal insufficiency showed absent response of serum cortisol level.

*Secondary adrenal insufficiency usually shows blunted response at 60 minutes, but the cortisol level further increase at 24 hours. Occasionally, the secondary adrenal insufficiency demonstrated normal response at 60 minutes.

(6) Insulin hypoglycemic stimulation test

*To determine growth hormone secretion and the hypothalamic-pituitary-adrenal axis

*The test is contraindicated in patients with old aged, cardiovascular disease or seizure disorder. In suspected hypopituitarism cases(with adrenal insufficiency), the

insulin dosage should be decreased(0.05u/kg) or not to perform this test in these patients.
*Close monitoring of vital signs, S/S of hypoglycemia by doctors is strongly necessary throughout the whole examination.
Procedure
*Regular insulin is given 0.15u/kg intravenously and check the glucose, GH, cortisol at 0, 30, 60, 90, 120 minutes.(Overnight fast before examination)
*If the patient suffered from severe hypoglycemia during examination, the iv glucose should be pushed , but the blood sampling examination should be continued until 120minutes.(The mild hypoglycemia S/S should also not terminate the test)
*Check the serum glucose, cortisol and GH level at each time points
*A meal should given after test finishment.
Interpretation
*GH usually peaks at 40-90 minutes after insulin injection, and it should increase to an absolute level of 10 ng/ml.Value less than 7 ng/ml is considered abnormal and 7-10 ng/ml is equivocal. For appropriate stimulation of GH secretion, a fall of BS at least 50% from baseline(i.e. 40mg/dl) is necessary.
*A peak cortisol level greater than 18-20μg/dl implies intact pituitary adrenal response.

(7) Thyroid sonography

甲狀腺是相當表淺之內分泌腺體，因而在超音波檢查應用上是相當容易，且不需任何準備動作。在檢查時病人是以平躺為宜。然而偶而遇到呼吸衰竭病人或有氣管內管加上呼吸器時，由於在臨床上急於知道甲狀腺腫大之原因，我們也可在半臥情況下施予檢查。由於甲狀腺解剖位置表淺且不大。因而可使用高解像力之探頭，在診斷上則可探測較小之病變。早期之超音波使用5Mhz之Grand Scale儀器，解像力較不佳。而目前使用7.5~10 MHz Real Time之超音波，對於小於0.5公分之病變，偵測效果仍不錯。 我們目前使用HP，以10 MHz Real Time來偵測甲狀腺結節。病人在平躺後以枕頭墊在頸部下方，使前頸呈伸展狀態。在簡單說明檢查步驟後，將塗在前頸部後，先以橫向方式掃瞄，由病人右方至左方掃瞄整個甲狀腺。再以縱向方式掃瞄。在大致了解所檢查甲狀腺解剖位置後，再對可疑之病變位置進行掃瞄。對於異常之位置，探究其病變之性質，大小及深度。

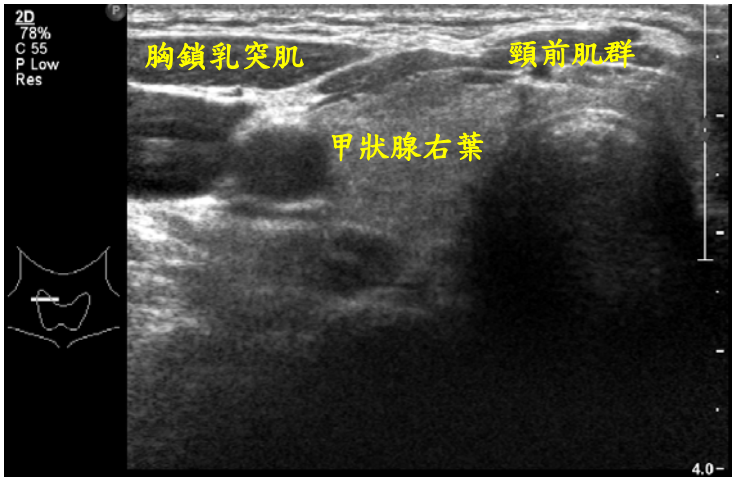
超音波在甲狀腺與副甲狀腺疾病所扮演的角色

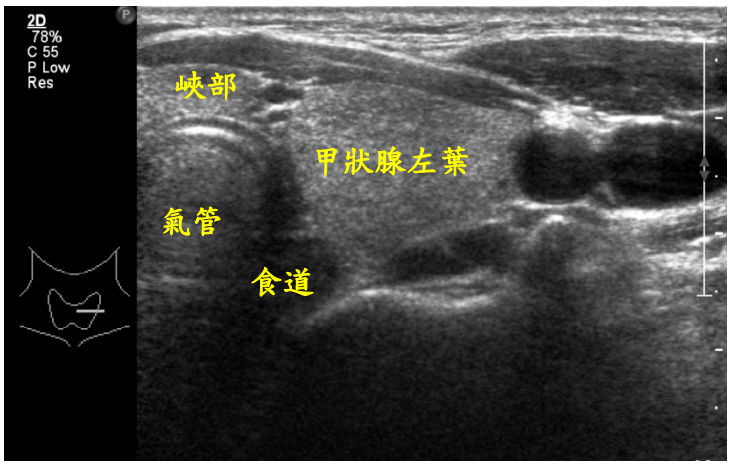
甲狀腺與副甲狀腺兩個內分泌腺體，因其位置較為表淺，各式病變容易被超音波偵測到。據 Semin Roentgenol 2013 年一月報導: 題 甲狀腺與副甲狀腺影像學 (作者 J. Lee 等人)，該文章主要簡介如何利用超音波診斷甲狀腺與副甲狀腺疾病。本篇文章影像皆為撰寫作者自己收集之影像資料。

正常甲狀腺解剖構造及超音波影像

甲狀腺是人體最大的內分泌器官，形狀似蝴蝶，其位置主要包覆在頸部環狀軟骨下方，氣管軟骨之上的氣管兩旁。甲狀腺構造可分為左右兩葉和峽部。兩葉各約一至二公分厚，二至三公分寬，四公分長。一般右葉比左葉略大，左葉的下方有食道通過。中間的峽部較小，長約兩公分，只有零點五公分厚。正常成人的甲狀腺重量介於十五克至二十克間，當甲狀腺腫大（thyroid goiter）時可重達上百克。甲狀腺因其位置表淺且沒有被骨頭或空氣遮蔽，故可以藉由超音波做清楚且全面評估。在正常狀態下，因甲狀腺為致密均勻實質器官，所以它的超音波屬於中等回音，回音強度較週邊肌肉組織高，。超音波橫切面時，甲狀腺的兩側可見總頸動脈及頸靜脈，前方和前側方可見呈低回音的頸前肌群和胸鎖乳突肌。而左葉內側後方可以看見食道，甲狀腺後方有四個副甲狀腺，但正常情況不易看見。

圖一、正常甲狀腺構造





正常的甲狀腺為均質的中回音，回音強度較週邊肌肉組織，左葉內下方可見食道，可請病人吞嚥口水，超音波下可見食道蠕動。

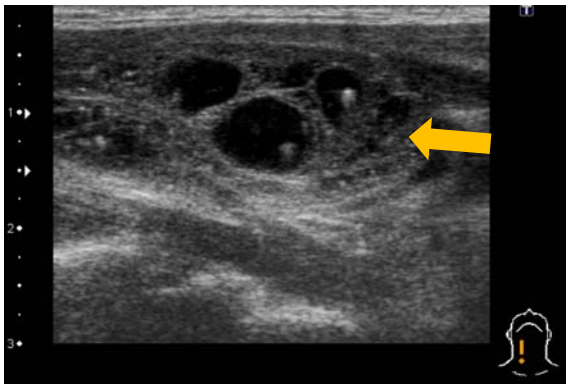
常見甲狀腺疾病與超音波影像

甲狀腺相關疾病包含甲狀腺結節、甲狀腺癌及甲狀腺機能亢進或低下等，臨床上除了利病史詢問、理學檢查和生化與內分泌功能檢查來加以診斷外，也可以運用超音波做為輔助之用。以下將甲狀腺超音波於各疾病的特色及運用加以介紹。

甲狀腺結節

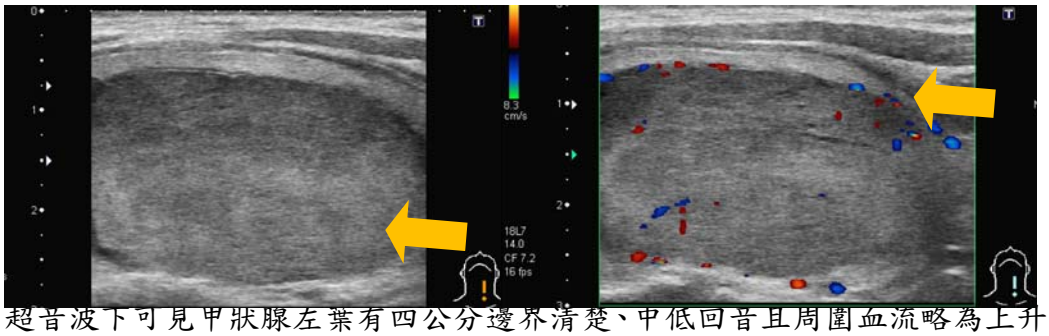
結節指的是甲狀腺長出之腫塊，內容物可能包含固體或液體，病理分類上大部分是良性的組織，只有少數為惡性--即甲狀腺癌。根據文獻統計，用手觸診約有 4%的人可發現有甲狀腺結節，如以超音波評估，則有高達 30%至 50%的人有甲狀腺結節，甚至甲狀腺內的結節約二至三釐米即可在超音波下被看到。甲狀腺結節盛行率可能會隨碘缺乏攝取及年紀上升而增加。一般而言甲狀腺結節多無明顯症狀，但結節較大時，可能會壓迫氣管、食道、神經而導致呼吸困難、吞嚥困難或聲音嘶啞等症狀，如結節合併出血時可能會迅速變大而產生局部脹痛不適。大多的結節沒有伴隨甲狀腺功能異常，但有些會增加甲狀腺素之分泌，產生甲狀腺機能亢進的臨床症狀，稱為毒性甲狀腺腺瘤（toxic adenoma）。臨床上超音波可幫助評估結節的大小形狀、邊界、回音、固體或液體組成比例、血流分布和強度及有無鈣化情形。良性的結節一般邊界清楚、包膜完整、沒有或些微的血流增加，結節內可能為固體、液體或兩者並存，內容物只有液體多為良性的囊腫（cyst），囊腫內細微的結晶可能在超音波下呈現彗星狀（comet tail sign）。固體的結節可能為中或略低之回音，合併囊腫或鈣化的產生。粗鈣化點(macrocalcification)如蛋型（eggshell）的鈣化，一般不會增加診斷惡性腫瘤之比率。

圖二、甲狀腺囊腫



超音波縱切面下可見甲狀腺右葉有多發性的甲狀腺囊腫，可見囊腫內的膠體(colloid)呈現彗星狀(comet tail sign)

圖三、良性甲狀腺結節

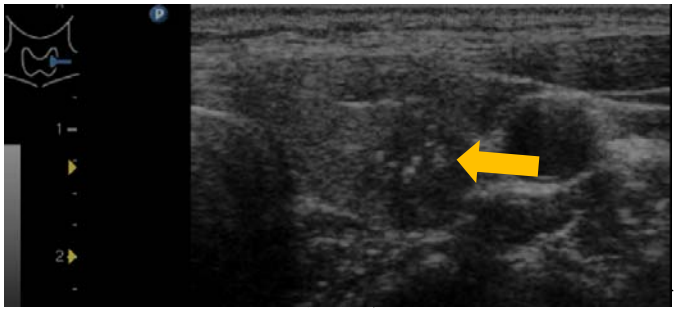


超音波下可見甲狀腺左葉有四公分邊界清楚、中低回音且周圍血流略為上升之結節，開刀確認為良性甲狀腺結節。

甲狀腺癌

常見的甲狀腺癌有濾泡癌（papillary carcinoma）、乳突癌（follicular carcinoma）、髓狀癌（medullary carcinoma）及大多發生於老人家且惡性度高的分化不良癌（anaplastic carcinoma）。初期甲狀腺癌多無明顯症狀，可能因有淋巴轉移產生頸部腫塊時才就醫。隨著病情進展，腫塊會侵犯周圍組織時，吞嚥時甲狀腺腫會移動的程度會減低，甚至可伴隨呼吸與吞嚥困難、聲音嘶啞、頸交感神經節受壓，甚至是遠端轉移之症狀。惡性腫瘤在一般超音波成像常有以下幾項特色：橫切面的高度大於寬度（taller than wide），因生長快速導致結節邊界不清楚(irregular margins)、無完整包膜之影像（absence of halo），腫瘤內部呈現低回音（hypoechoic）、與乳突癌相關之小鈣化點（microcalcification）。另外也可以評估有無頸部淋巴結腫大及對週邊構造之壓迫或侵犯程度。若搭配杜普勒超音波（Doppler ultrasound）則可觀察是否有結節內血流增加的情形（increased internal or central flow）。因惡性細胞沒有正常細胞之規則排列，且腫瘤細胞較為緻密，所以有研究利用彈性超音波（elastography），對結節的軟硬度進行評估，提高超音波對良惡性結節的診斷力。

圖四、甲狀腺乳突癌



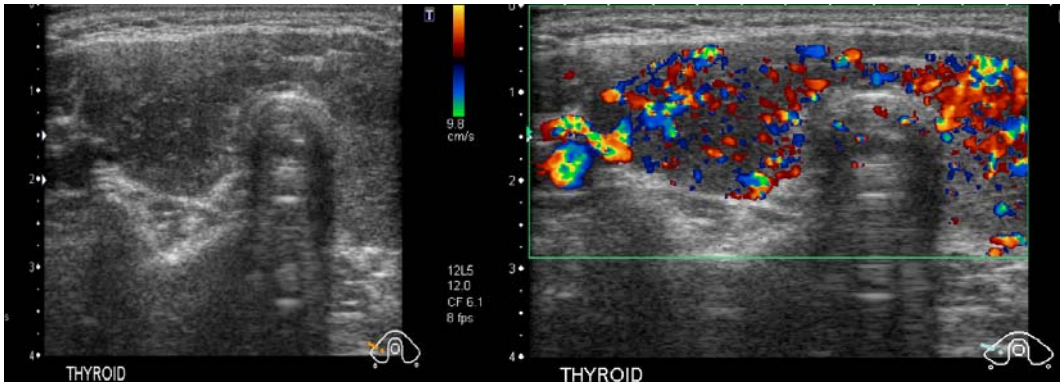
且合併有小鈣化點，細針穿刺診斷為甲狀腺乳突癌

截至目前，單憑超音波影像仍無法明確診斷結節的良惡性，目前國際間仍公認細針穿刺細胞學(Fine needle aspiration cytology)為一敏感、便利且具經濟效益的診斷方式。根據美國甲狀腺學會建議：大於一公分的實質結節應做甲狀腺細針穿刺。介於五釐米至一公分的結節如有疑似惡性腫瘤的特徵或高危險之病史也應做細針穿刺。結節較小時(小於一公分)可以利用超音波導引細針穿刺（Ultrasound-guided fine-needle aspiration）。

甲狀腺炎

甲狀腺炎包括與自體免疫相關之葛瑞夫氏症（Graves' disease）及橋本氏甲狀腺炎(Hasimoto' s thyroiditis)、細菌感染導致的化膿性甲狀腺炎(Suppurative thyroiditis)和病毒感染導致的亞急性甲狀腺炎(Subacute thyroiditis)。典型葛瑞夫氏症的超音波成像為甲狀腺腫，合併回音降低及異質化，杜普勒超音波呈現顯著增加之血流。

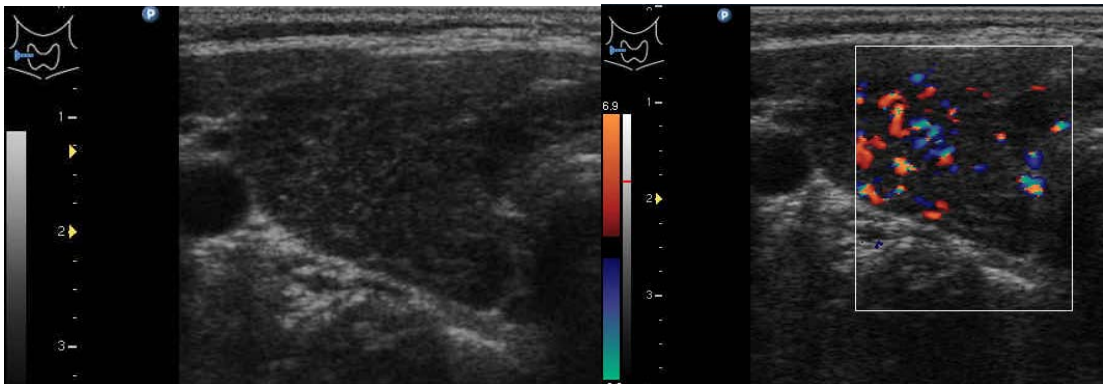
圖五、葛瑞夫氏症



超音波下可見甲狀線呈現瀰漫異質性低回音，杜普勒超音波下血流顯著增加。

橋本氏甲狀腺炎，因甲狀腺遭自體免疫抗體破壞，超音波一般可見異質化且回音降低之甲狀腺，杜普勒超音波之血流可能從低至高有不同的變化。

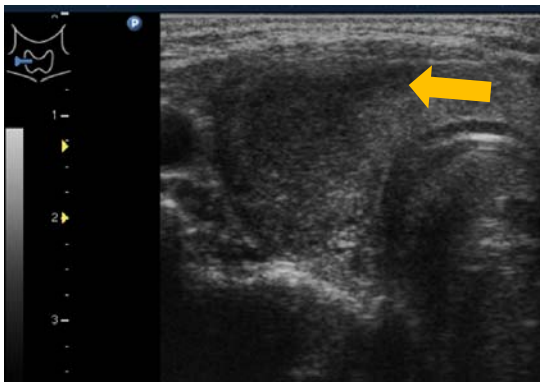
圖六、橋本氏甲狀腺炎



甲狀腺超音波下可見瀰漫性異質性低回音與纖維化間隔，杜普勒超音波下血流常有不等程度之變化。

亞急性甲狀腺炎多認為病毒感染後直接或間接造成的甲狀腺發炎，臨床常見發生在上呼吸道感染後，有甲狀腺腫痛（可能單側、雙側或兩側先後受影響）、發燒、發炎指數顯著上昇的情形。超音波下可見甲狀腺受影響的區域有不均勻且邊界且不規則的回音降低，杜普勒超音波下之血流並不會顯著上昇。在疾病緩解後持續追蹤超音波可發現低回音的病灶會在數個月後逐漸回復至原本均質的中等回音。另可考慮做細針穿刺與甲狀腺癌做鑑別診斷，通常細胞學檢查可見多核巨細胞及淋巴球。

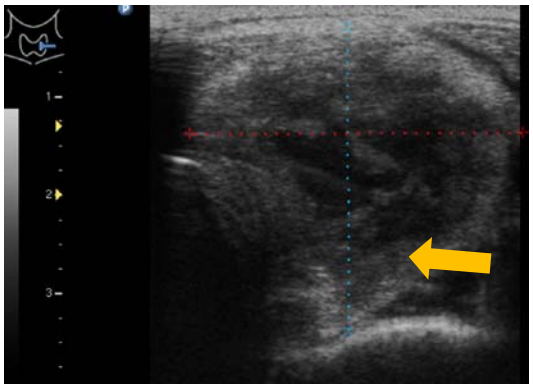
圖七、亞急性甲狀腺炎



甲狀腺超音波下可見受影響的部分呈異質性低回音但杜普勒超音波下血流並未顯著上升，通常數月後追蹤，低回音的部位會逐漸恢復為原本均質的中等回音。

化膿性甲狀腺炎，主因為病人有先天結構之異常（如梨狀竇廔管 pyriform sinus fistula）或免疫力不全之患者，則甲狀腺有可能被細菌、結核菌或黴菌感染而導致化膿性甲狀腺炎。疾病初期超音波下可見甲狀腺內有邊界略微模糊的低回音病灶，隨病程進展超音波可見甲狀腺內膿瘍形成，細針抽吸可見膿狀物並可以培養病原菌，一般如有合併先天結構異常需做手術切除避免復發。

圖八、化膿性甲狀腺炎



甲狀線左葉可見近三公分邊界不規則異質低回音區塊，細針抽吸為膿狀物。

正常副甲狀腺解剖構造及超音波影像

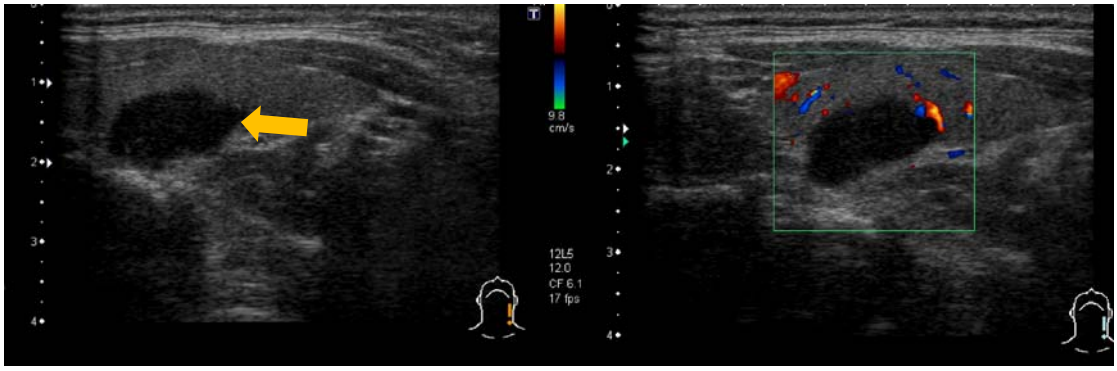
大部份的人(約 80%)具有 4 個副甲狀腺，但其他 15%的人會有 5 個甚至更多的副甲狀腺體，反之 5%的人僅有 3 個副甲狀腺體。每個副甲狀腺體大小一般約 35 毫克左右，約為 5x3x1 毫米小大。一般典型狀態下 4 個副甲狀腺可分為上與下，各有 2 個腺體，其中上副甲狀腺體處於甲狀腺中三分之一的後兩側，而下副甲狀腺體則位於兩側甲狀腺下緣的下方或後方或側面處。但約有 1-3%的副甲狀腺位置屬於異位性質，可能位於縱隔腔或甲狀腺實質內或頸動脈鞘附近。副甲狀腺體在人體內主要的功能為分泌副甲狀腺荷爾蒙並用以調節體內血鈣與磷的濃度。一般而言，副甲狀腺腺體因很小，再加上其音波回音度與甲狀腺實質類似，所以不會被辨認出來。

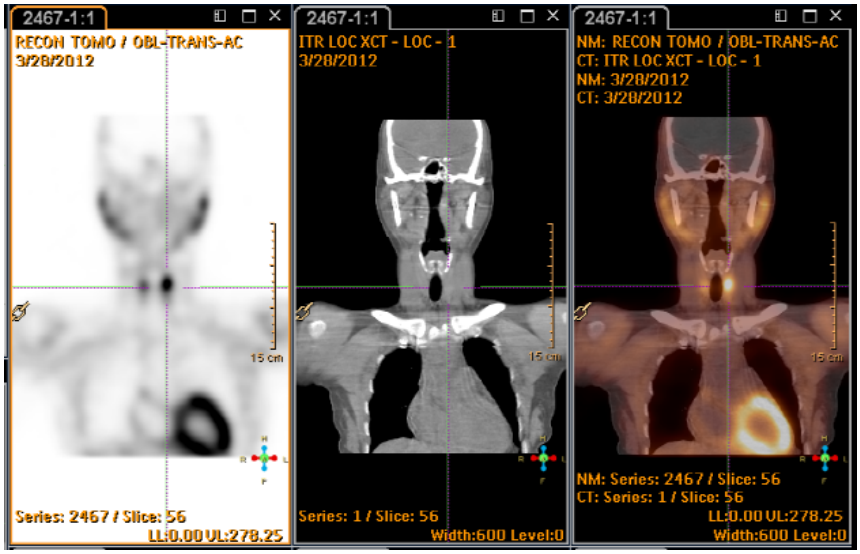
副甲狀腺機能亢進與副甲狀腺腫瘤

當副甲狀腺產生原發性的副甲狀腺機能亢進時，會因為副甲腺荷爾蒙過度分泌，導致血鈣濃度增加而產生如骨質密度下降、尿路結石、神經肌肉系統、腸道系統、心血管系統，甚至中樞神經系統等疾病發生。副甲狀腺機能亢進大多為單一副甲狀腺腫瘤導致，但也可由於副甲狀腺體增生或多顆副甲狀腺腫瘤，甚至副甲狀腺癌所引發產生。

當副甲狀腺變成腫瘤時，超音波影像會呈現一較低回音，並與甲狀腺實質界線明顯的均質腫塊。有時副甲狀腺腫瘤可於腫瘤內呈現囊狀的變化(約 1-2%)。當副甲狀腺腫瘤位置是屬於異位性的時候，可能無法與頸部淋巴節或甲狀腺內的節結來區分，或甚至無法由超音波辨認到。約有 1%的副甲狀腺腫瘤為副甲腺癌時(約 1%)，其超音波特性較良性副甲腺腫瘤，顯得回音較不均質且邊界不明顯，腫塊本身之高度會大於寬度。整體而言，依過去之研究統計，副甲狀腺瘤能被超音波偵測到的比率約為 70~90%左右(平均為 80%左右），但是如果是兩個副甲狀腺腫瘤，甚至是副甲狀腺增生 其被超音診斷的比例分別會降至 35%與 16%左右。此外使用超音波來偵測副甲狀腺瘤時。也可運用細針穿刺細胞檢查，亦有助副甲狀腺機能亢進的術前診斷。

圖九、副甲狀腺腫瘤





甲狀腺左葉後上方可見一低回音邊界清楚之結節，臨床上生化檢驗合併有高血鈣與副甲狀腺素上升，核醫掃描確認為副甲狀腺腫瘤。

其它甲狀腺與副甲狀腺超音波發展方向

近年更發展甲狀腺超音波電腦輔助診斷系統，可以從影像處理系統中擷取腫瘤輪廓，輔助臨床診斷與決策。而利用超音波導引執行甲狀腺腫瘤射頻燒灼術(radiofrequency ablation)等技術之發展，或利用超音波導引於病變部位注射藥物(如甲狀腺癌之頸部轉移淋巴節或副甲狀腺腫瘤注射酒精)，以達免開刀的治療目的。這些運用都使得超音波在甲狀腺與副甲狀腺相關疾病的診斷及治療上日趨重要。

結論

超音波相對於其他現有臨床常用的醫學影像系統（如: X 光、電腦斷層掃描、核磁共振攝影、核醫影像等），具有低價格、非侵入式、無放射性危險、即時影像、釐米級的影像解析度、可攜性、並可量測血流等優點，所以已成為診斷表淺內分泌腺體疾病(如甲狀腺與副甲狀腺)的重要工具。為能有效發現甲狀腺與副甲狀腺疾病，醫療人員需充分了解此兩個內分泌腺體的解剖學位置與超音波操作上的技

巧。之後了解各式疾病在超音波上的影像特點，並配合其它臨床上的檢查結果，而對病患的疾病做出最適當的判斷。當然我們也必需理解超音波對於甲狀腺或副甲狀腺疾病診斷的侷限性，而需搭配其它的影像檢查工具如核醫學檢查等。

(8) Thyroid fine needle aspiration

1. use 10cc syringe, 20-22-gauge needle
2. fixed the nodule between the second and third digits of left hand and insert the needle with the right hand
3. for <1.5 cm nodule, simply inserting th needle into the nodule is a reasonable goal; for larger nodules, peripheral subcapsular parts of the nodule should be sampled rather than the center.
4. Suction: for tissue disruption, simply application of suction by pulling the plunger of the syringe back to 6-7 cm is often unsatisfactory; moving the needle in and out has better result and has much the same effect as using mechanical device (figure 2.3-2.4)
5. The total procedure should be sufficient to make aspiration appear in the hub of the needle but not in the barrel of the syringe
6. Smears: after suction, the needle is removed and the plunger is withdrawn a couple of milliliters. The needle is reaffixed and the specimen is expressed onto the slide. Then compressed between two slides and smeared.

(9) Lower limb doppler sonography

ABI (ankle brachial index)—for peripheral artery disease detection.

1. using Medacord PVL enhanced machine, 8 MHz probe for artery signal detection
2. put the cuff over arm and inflate the cuff until the pressure is 10 to 15 mmHg above the point where arterial signal stops
3. then drop the pressure 3 to 5 mmHg pre second until the arterial signal returns again
4. put the cuff over ankle area then put the probe over dorsalis pedis artery, posterior tibial artery respectively. These two areas represent ankle pressure.
5. For calculating ABI: highest ANK/ highest ARM

Example: Rt brachial	132	Lt brachial	128
Rt PTA	82	Lt PTA	140
Rt DPA	90	Lt DPA	138
Rt ABI	90/132= 0.68		
Lt ABI	140/132= 1.06 (>1)		

6. a normal ABI is > 0.91, an ABI <0.91 may indicate significant arterial obstruction.

新陳代謝科學習進度及考核表

台中榮民總醫院　內科部　新陳代謝科

高年級醫學生訓練紀錄表

卡號：　　姓名：　　起迄時間：　　年　月至　　年　月

項　　目	標準次數	實際次數	評分	複考
病歷寫作－DM, poor control	6			
HHNK, DKA	2			
Other endocrine disease	2			
門診教學	2			
晨會病歷報告	3			
病歷討論	2			
理學檢查	10			
甲狀腺理學檢查	10			
自主神經功能檢查	5			
周邊血管檢查	5			
學習甲狀腺超音波及細針穿刺檢查	10			

學習態度評分	
負責精神評分	
綜合評分	
評語	

考評　　簽章

台中榮民總醫院　內科部　新陳代謝科

第一年住院醫師訓練紀錄表

卡號：　　姓名：　　起迄時間：　　年　月至　　年　月

項　　目	標準次數	實際次數	評分	複考
糖尿病診斷	10			
糖尿病急性併發症的診斷處理	10			
糖尿病慢性併發症的診斷處理	10			
糖尿病病患營養及飲食衛教	10			
降血糖藥物使用原則	10			
血糖機使用	5			
高血脂症	5			
期刊閱讀	1			
學習態度評分				
負責精神評分				
綜合評分				
評語				

考評　　簽章

台中榮民總醫院　內科部　新陳代謝科

第二年住院醫師訓練紀錄表

卡號：　　姓名：　　起迄時間：　　年　月至　　年　月

項　　目	標準次數	實際次數	評分	複考
第一年住院醫師訓練項目				
甲狀腺理學檢查	10			
甲狀腺功能檢查判讀	10			
高、低甲狀腺功能症診斷及處理	10			
甲狀腺節結處理	10			
副甲狀腺疾病診斷及處理	1			
腎上腺疾病診斷及處理	1			
期刊閱讀	1			
學習態度評分				
負責精神評分				
綜合評分				
評語				

考評　　簽章

台中榮民總醫院　內科部　新陳代謝科

第三年住院醫師訓練紀錄表

卡號：　　姓名：　　起迄時間：　　年　月至　　年　月

項　　目	標準次數	實際次數	評分	複考
第一、二年住院醫師訓練項目				
腦下垂體疾病診斷及處理	1			
性腺疾病診斷及處理	1			
動態性內分泌功能檢查判讀	5			
甲狀腺超音波操作及判讀	5			
甲狀腺細針穿刺操作	5			
期刊閱讀	1			
學習態度評分				
負責精神評分				
綜合評分				
評語				

考評　　簽章

新陳代謝科資深住院醫師訓練進度報告表

姓名：＿＿＿＿　職別：第＿年住院醫師　導師：＿＿＿＿

訓練開始日期：　年　月　日　填表日期：　年　月　日

A. 學習內容

臨床工作與技能訓練	**應達成目標**	**實際完成數量**
新陳代謝科主治醫師跟診次數	每位 VS 至少一年內跟診 6 次 (共 36 次)	累積　次
門診人次	≧150/季	例/季
會診人次	≧15/季	例/季
住院病患新陳代謝疾病暨內分泌急症照護參與	≧5 例/月	例/月
住院醫師與實習醫師教學活動	≧3 次/月	次/月
甲狀腺超音波	≧30 例/月	例/月
甲狀腺細針穿刺	≧15 例/月	例/月
內分泌功能檢查及判斷	≧3 例/季	例/季
參與相關科室活動（如下）		**實際完成數量**
糖尿病護理與營養衛教		例/季
糖尿病眼底攝影判讀		例/季
甲狀腺細胞學判讀		例/季
內分泌疾病核醫學造影檢查判讀		例/季
一般外科甲狀腺與副甲狀腺疾病病理討論會		例/季
小兒科新陳代謝門診跟診次數		次/季

學術研究		
EBM 案例實作	1/年	附件
雜誌選讀會議	12/年	附件
臨床試驗研究	1/年	附件
學會參與或報告	2/年	附件
期刊發表	1/年	附件

B. 自我整體學習進度評估　　(請標記)　　備　　註

合乎進度　□

超前進度　□

落後進度　□

C. 學習護照完成百分比例　_____%

實習醫學生學習核心課程表

一、核心訓練課程---症狀或徵候	教師評量		
	A	B	備註
1. 體重減輕			
□ 病史詢問的完整性及適當的鑑別診斷	☐	☐	
□ 能開立適當的檢查項目	☐	☐	
□ 能判斷是否需要其他科處理	☐	☐	
二、核心訓練課程---病態或疾病			
1.糖尿病			
□ 能陳述的糖尿病診斷標準及治療目標	☐	☐	
□ 能概述糖尿病小血管與大血管併發症	☐	☐	
□ 能開立基本的檢查項目，包括血糖及糖化血色素及血脂肪及肝腎功能及心電圖及尿液檢查及眼底檢查等	☐	☐	
□ 能說明糖尿病常用藥物機轉、開立適當的降血糖或血脂藥物處方並依檢查結果調整	☐	☐	
三、核心訓練課程---臨床技能			
1. 理學檢查技巧			
□ 能做全身一般性的理學檢查（包括測量生命徵象、意識狀態的評量、皮膚、頭頸部、眼睛、耳鼻喉、淋巴結、胸肺、心血管及周邊脈搏、背部、泌尿生殖器、四肢及骨骼關節、神經學、精神狀態、認知評量等檢查。）	☐	☐	
□ 能做完整的甲狀腺理學檢查（包括視、聽、敲、觸診）	☐	☐	
□ 能做正確的足部神經感覺檢查及自主神經病變檢查	☐	☐	
2. 糖尿病衛教			
□ 能開立適當的糖尿病飲食醫囑及做口頭衛教（含低血糖衛教）	☐	☐	
□ 能實施胰島素抽藥或注射(含空針與筆型胰島素注射器)	☐	☐	
□ 能操作血糖機自我檢驗血糖	☐	☐	
3. 實驗診斷技巧與判讀			
□ 能做血液檢體採取（包括適當的儲存與傳送及相關安全事項）	☐	☐	
□ 能開立及判讀各糖尿病血液、尿液檢查或內分泌功能檢查的基本檢查項目	☐	☐	
四、選修訓練課程（未選修者請勾選於後方 X 處）			
1. 甲狀腺超音波及針吸細胞學檢查			
□ 能說明各項檢查的適應症、禁忌症及併發症	☐	☐	
□ 觀察甲狀腺超音波檢查及細針抽吸檢查(至少五例)	☐	☐	
2. 足臂動脈超音波及非散瞳眼底照相檢查			
□ 觀察足臂動脈超音波及眼底照相檢查(各至少三例)	☐	☐	
□ 能初步判斷是否有周邊動脈阻塞疾病	☐	☐	
□ 能初步判斷是否有糖尿病眼底病變	☐	☐	

內科住院醫師學習護照新陳代謝科部份

新　陳　代　謝　科											
住院照護	必修(例數)	病歷號碼	日期	親自照護	見習	指導醫師	病歷號碼	日期	親自照護	見習	指導醫師
糖尿病 (Diabetes mellitus) and its complications	5										
糖尿病足感染症 (Diabetic foot infection)	3										
與感染科合計											
糖尿病酮酸中毒 (Diabetic ketoacidosis) 與 ICU 合計	1										
高滲透壓高血糖非酮酸性昏迷 (Hyperosmolar hyperglycemic nonketotic coma, HHNK) 與 ICU 合計	1										
病態性肥胖 (Morbid obesity)											
高血脂症 (Hyperlipidemia)											
腦垂體腫瘤 (Pituitary tumor)											
泛腦垂體功能低下症 (Panhypopituitarism)											
甲狀腺機能亢進 (Hyperthyroidism)											
甲狀腺機能低下 (Hypothyroidism)											
庫欣氏症 (Cushing syndrome)											
腎上腺機能不足 (Adrenal insufficiency)											
皮質醛酮症 (Aldosteronism)											
嗜鉻細胞瘤 (Pheochromocytoma)											
骨質疏鬆 (Osteoporosis)											
高尿酸血症與痛風 (Hyperuricemia and gout) 與免疫風濕科合計											